UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

Form 10-Q

(Mark One)

x QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the Quarterly Period Ended March 31, 2010

OR

o TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF SECURITIES EXCHANGE ACT OF 1934

For the transition period from to

Commission file number 0-19125

Isis Pharmaceuticals, Inc.
(Exact name of Registrant as specified in its charter)

Delaware	**33-0336973**
(State or other jurisdiction of incorporation or organization)	(IRS Employer Identification No.)

1896 Rutherford Road, Carlsbad, CA 92008
(Address of principal executive offices, including zip code)

760-931-9200
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: **None**

Securities registered pursuant to Section 12(g) of the Act:

Common Stock, $.001 Par Value

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes x No o

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes o No o

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See definition of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer x	Accelerated filer o
Non-accelerated filer o (Do not check if a smaller reporting company)	Smaller reporting company o

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12(b)-2 of the Securities Exchange Act of 1934). Yes o No x

The number of shares of voting common stock outstanding as of May 3, 2010 was 99,088,156.

ISIS PHARMACEUTICALS, INC.
FORM 10-Q

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TRADEMARKS

Isis Pharmaceuticals® is a registered trademark of Isis Pharmaceuticals, Inc.
Regulus Therapeutics™ is a trademark of Regulus Therapeutics Inc.
Ibis T5000™ is a trademark of Ibis Biosciences, Inc.
Vitravene® is a registered trademark of Novartis AG.

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ISIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED BALANCE SHEETS
(in thousands, except share data)

	March 31, 2010 (Unaudited)	December 31, 2009
ASSETS		
Current assets:		
Cash and cash equivalents	$ 98,590	$ 105,255
Short-term investments	420,529	469,057
Contracts receivable	1,904	10,899
Inventories	2,601	2,768
Other current assets	6,791	8,147
Total current assets	530,415	596,126
Property, plant and equipment, net	36,171	27,338
Licenses, net	14,007	14,542
Patents, net	15,919	15,909
Deposits and other assets	3,211	3,269

Total assets	$ 599,723	$ 657,184
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 4,843	$ 4,696
Accrued compensation	2,971	7,135
Income taxes payable	—	7,323
Accrued liabilities	9,371	12,339
Current portion of long-term obligations	4,020	4,270
Current portion of deferred contract revenue	70,890	75,681
Total current liabilities	92,095	111,444
2 5/8% convertible subordinated notes	126,986	125,100
Long-term obligations, less current portion	4,474	11,478
Long-term financing obligation	10,147	—
Investment in Regulus Therapeutics Inc.	127	—
Long-term deferred contract revenue	81,457	107,097
Total liabilities	315,286	355,119
Stockholders' equity:		
Common stock, $0.001 par value; 200,000,000 shares authorized, 99,077,428 and 98,850,934 shares issued and outstanding at March 31, 2010 and December 31, 2009, respectively	99	99
Additional paid-in capital	988,053	985,620
Accumulated other comprehensive income	1,379	2,153
Accumulated deficit	(705,094)	(696,150)
Total Isis Pharmaceuticals, Inc. stockholders' equity	284,437	291,722
Noncontrolling interest in Regulus Therapeutics Inc.	—	10,343
Total stockholders' equity	284,437	302,065
Total liabilities and stockholders' equity	$ 599,723	$ 657,184

See accompanying notes.

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ISIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF OPERATIONS
(in thousands, except for per share amounts)
(Unaudited)

	Three Months Ended March 31,	
	2010	2009(1)
Revenue:		
Research and development revenue under collaborative agreements	$ 28,556	$ 29,685
Licensing and royalty revenue	1,370	1,891
Total revenue	29,926	31,576
Expenses:		
Research and development	31,987	28,541
General and administrative	2,819	3,677
Total operating expenses	34,806	32,218
Loss from operations	(4,880)	(642)
Other income (expense):		
Equity in net loss of Regulus Therapeutics Inc.	(1,486)	—
Investment income	955	2,134
Interest expense	(3,237)	(3,081)
Gain (loss) on investments, net	(1,010)	58
Loss from continuing operations, before income tax expense	(9,658)	(1,531)
Income tax expense	—	(160)
Net loss from continuing operations	(9,658)	(1,691)
Discontinued operations:		
Loss from discontinued operations	—	(29)
Gain on sale of Ibis Biosciences, Inc., net of tax	—	187,025
Net income from discontinued operations, net of tax	—	186,996
Net income (loss)	(9,658)	185,305

Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	—	913
Net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (9,658)	$ 186,218
Basic and diluted net income (loss) per share:		
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (0.10)	$ (0.01)
Net income from discontinued operations	—	1.92
Basic and diluted net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (0.10)	$ 1.91
Shares used in computing basic and diluted net income (loss) per share	99,013	97,521

(1) During the preparation of the year end 2009 annual tax provision, we determined that certain tax items had been attributed to discontinued operations that are appropriately associated with continuing operations. As a result, we revised the tax provisions reflected in each of the first three quarters during 2009 to reflect the correction of this allocation. The historical condensed consolidated statement of operations for the three months ended March 31, 2009 reflects the revised tax provisions.

See accompanying notes.

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ISIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS
(in thousands)
(Unaudited)

	Three Months Ended March 31,	
	2010	2009(1)
Net cash used in operating activities	$ (21,691)	$ (34,398)
Investing activities:		
Purchases of short-term investments	(125,598)	(224,186)
Proceeds from the sale of short-term investments	158,621	98,973
Purchases of property, plant and equipment	(11,009)	(3,141)
Proceeds from land sold to BioMed	10,147	—
Reduction of cash due to deconsolidation of Regulus Therapeutics Inc. upon adoption of a new accounting standard	(16,228)	—
Acquisition of licenses and other assets	(516)	(210)
Purchases of strategic investments	(459)	(349)
Net cash provided by (used in) investing activities	14,958	(128,913)
Financing activities:		
Net proceeds from issuance of equity	1,031	6,143
Excess tax benefits on share-based compensation	—	52
Proceeds from equipment financing arrangement	—	2,705
Principal payments on debt obligations	(963)	(517)
Proceeds from sale of Ibis Biosciences, Inc. to Abbott Molecular Inc.	—	175,000
Proceeds from Alnylam's capital contribution to Regulus Therapeutics Inc.	—	10,000
Net cash provided by financing activities	68	193,383
Net increase (decrease) in cash and cash equivalents	(6,665)	30,072
Cash and cash equivalents at beginning of period	105,255	223,985
Cash and cash equivalents at end of period	$ 98,590	$ 254,057
Supplemental disclosures of cash flow information:		
Interest paid	$ 2,281	$ 2,250
Income taxes paid	$ 7,700	$ 350
Supplemental disclosures of non-cash investing activities:		
Amounts accrued for capital and patent expenditures	$ 836	$ 5,016

(1) During the preparation of the year end 2009 annual tax provision, we determined that certain tax items had been attributed to discontinued operations that are appropriately associated with continuing operations. As a result, we revised the tax provisions reflected in each of the first three quarters during 2009 to reflect the correction of this allocation. The historical condensed consolidated statement of cash flows for the three months ended March 31, 2009 reflects the revised tax provisions.

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
March 31, 2010
(Unaudited)

1. Basis of Presentation

The unaudited interim condensed consolidated financial statements for the three month periods ended March 31, 2010 and 2009 have been prepared on the same basis as the audited financial statements for the year ended December 31, 2009. The financial statements include all normal recurring adjustments, which we consider necessary for a fair presentation of the financial position at such dates and the operating results and cash flows for those periods. Results for the interim periods are not necessarily indicative of the results for the entire year. For more complete financial information, these financial statements, and notes thereto, should be read in conjunction with the audited financial statements for the year ended December 31, 2009 included in our Annual Report on Form 10-K filed with the Securities and Exchange Commission ("SEC").

The condensed consolidated financial statements include the accounts of Isis Pharmaceuticals, Inc. ("we", "us" or "our") and our wholly owned subsidiaries, Isis USA Ltd. and Symphony GenIsis, Inc. In addition to our wholly owned subsidiaries, our condensed consolidated financial statements include our equity investment in Regulus Therapeutics Inc., an entity we identified as a variable interest entity. Beginning in the first quarter of 2010, as a result of adopting a new accounting standard for identifying which enterprise has the power to direct activities of a variable interest entity, we concluded that we are no longer the primary beneficiary of Regulus. As such we have presented our share of Regulus' operating results on a separate line in our condensed consolidated statement of operations called "Equity in net loss of Regulus Therapeutics Inc." On our condensed consolidated balance sheet, we have presented our investment in Regulus on a separate line in the non-current liabilities section called "Investment in Regulus Therapeutics Inc." Prior to the adoption of the new accounting standard, we were the primary beneficiary of Regulus and as such we consolidated Regulus' financial results on a line-by-line basis. We have not reclassified amounts in the prior period financial statements to conform to the current period presentation. As a result of completing the sale of Ibis Biosciences, Inc. to Abbott Molecular Inc., or AMI, in January 2009, we presented Ibis' financial position and results of operations separately as discontinued operations in our condensed consolidated financial statements. All significant intercompany balances and transactions have been eliminated.

2. Significant Accounting Policies

Revenue Recognition

We generally recognize revenue when we have satisfied all contractual obligations and are reasonably assured of collecting the resulting receivable. We are often entitled to bill our customers and receive payment from our customers in advance of recognizing the revenue under current accounting rules. In those instances where we have received payment from our customers in advance of recognizing revenue, we include the amounts in deferred revenue on our condensed consolidated balance sheet.

Research and development revenue under collaborative agreements

We often enter into collaborations under which we receive non-refundable upfront payments for prior or future expenditures. We recognize revenue related to upfront payments ratably over our period of performance relating to the term of the contractual arrangements. Occasionally, we are required to estimate our period of performance when the agreements we enter into do not clearly define such information. The revenue we recognize could be materially different if different estimates prevail. To date, we have not had to make material adjustments to our estimates. We have made estimates of our continuing obligations on several agreements. Our collaborative agreements typically include a research and/or development project plan that includes the activities the agreement requires each party to perform during the collaboration and the party responsible for performing them. We estimate the period of time over which we will complete the activities for which we are responsible and use that period of time as our period of performance for purposes of revenue recognition and amortize revenue over such period. When our collaborators have asked us to continue performing work in a collaboration beyond the initial period of performance, we have extended our amortization period to correspond to the new extended period of performance. In no case have adjustments to performance periods and related adjustments to revenue amortization periods had a material impact on our revenue.

Our collaborations often include contractual milestones. When we achieve these milestones, we are entitled to payment, according to the underlying agreements. We generally recognize revenue related to milestone payments upon completion of the milestone's substantive performance requirement, as long as we are reasonably assured of collecting the resulting receivable, the amounts are not refundable and we have no future performance obligations related to the achievement of the milestone.

We often enter into revenue arrangements that contain multiple deliverables. In these cases, we recognize revenue from each element of the arrangement as long as we are able to determine a separate fair value for each element, we have completed our obligation to deliver or perform on that element and we are reasonably assured of collecting the resulting receivable.

As part of our Genzyme strategic alliance, in February 2008 Genzyme Corporation made a $150 million equity investment in us by purchasing five million shares of our common stock at $30 per share. The price Genzyme paid for our common stock represented a significant premium over the fair value of our stock. Using a Black-Scholes option valuation model, we determined that the value of the premium was $100 million, which represented value Genzyme gave to us to help fund the companies' research collaboration, which began in January 2008. We accounted for this premium as deferred revenue and are amortizing it along with the $175 million licensing fee that we received in June 2008 ratably into revenue until June 2012, which represents the end of our performance obligation based on the current research and development plan.

Licensing and royalty revenue

We often enter into agreements to license our proprietary patent rights on an exclusive or non-exclusive basis in exchange for license fees and/or royalties. We generally recognize as revenue immediately those licensing fees and royalties for which we have no significant future performance obligations and are reasonably assured of collecting the resulting receivable.

Short-term investments

We consider all liquid investments with maturities of 90 days or less when purchased to be cash equivalents. Our short-term investments have initial maturities of greater than 90 days from date of purchase. We classify our short-term investments as "available-for-sale" and carry them at fair market value based upon prices for identical or similar items on the last day of the fiscal period. We record unrealized gains and losses as a separate component of stockholders' equity and include net realized gains and losses in gain (loss) on investments in the condensed consolidated statement of operations. We use the specific identification method to determine the cost of securities sold.

We have equity investments in privately- and publicly-held biotechnology companies. We hold ownership interests of less than 20 percent in each of the respective companies except Regulus, our majority owned subsidiary, which we began accounting for using the equity method in the first quarter of 2010. Prior to 2010, we consolidated Regulus' financial results on a line-by-line basis. In determining if and when a decrease in market value below our cost in our equity positions is temporary or other-than-temporary, we examine historical trends in the stock price, the financial condition of the company, near term prospects of the company and our current need for cash. We record unrealized gains and losses related to temporary declines in the publicly-held companies as a separate component of stockholders' equity and account for securities in the privately-held companies, except for Regulus, under the cost method of accounting because we own less than 20 percent and do not have significant influence in their operations. When we determine that a decline in value in either a public or private investment is other-than-temporary, we recognize an impairment loss in the period in which the other-than-temporary decline occurs. During the first three months of 2010, we recognized a $1.0 million loss on investments primarily consisting of an $880,000 non-cash loss related to the other-than-temporary impairment of our equity investment in Antisense Therapeutics Limited and a $149,000 valuation allowance we recorded related to our investment in Excaliard Pharmaceuticals, Inc. slightly offset by realized gains on sales of our available-for-sale securities. Because realization of our Excaliard investment is uncertain we recorded a full valuation allowance. During the first three months of 2009, we recognized a $58,000 gain on investments relating to sales of our available-for-sale securities. We determined that there were no other-than-temporary declines in value of our investments during the first three months of 2009.

Inventory valuation

We capitalize the costs of raw materials that we purchase for use in producing our drugs because until we use these raw materials they have alternative future uses. We include in inventory raw material costs for drugs that we manufacture for our partners under contractual terms and that we use primarily in our clinical development activities and drug products. We can use each of our raw materials in multiple products and, as a result, each raw material has future economic value independent of the development status of any single drug. For example, if one of our drugs failed, we could use the raw materials allocated for that drug to manufacture our other drugs. We expense these costs when we deliver the drugs to our partners, or as we provide these drugs for our own clinical trials. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. We review inventory periodically and reduce the carrying value of items we consider to be slow moving or obsolete to their estimated net realizable value. We consider several factors in

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estimating the net realizable value, including shelf life of raw materials, alternative uses for our drugs and clinical trial materials and historical write-offs. We did not record any inventory write-offs during the first three months of 2010 and 2009. Total inventory, which consisted of raw materials, was $2.6 million and $2.8 million as of March 31, 2010 and December 31, 2009, respectively.

Patents

We capitalize costs consisting principally of outside legal costs and filing fees related to obtaining patents. We review our capitalized patent costs regularly to ensure that they include costs for patent applications that have future value. We evaluate costs related to patents that we are not actively pursuing and write off any of these costs. We amortize patent costs over their estimated useful lives of ten years, beginning with the date the United States Patent and Trademark Office issues the patent. For the first three months of 2010 and 2009, we recorded a non-cash charge of $68,000 and $186,000, respectively, which we included in research and development expenses, related to the write-down of our patent costs to their estimated net realizable values.

Long-lived assets

We evaluate long-lived assets, which include property, plant and equipment, patent costs, and licenses acquired from third parties, for impairment on at least a quarterly basis and whenever events or changes in circumstances indicate that the carrying amount of such assets may not be recoverable.

Equity Method of Accounting

On January 1, 2010, we adopted an accounting standard, which replaced the quantitative-based risks and rewards calculation for determining which enterprise, if any, has a controlling financial interest in a variable interest entity. The new approach focuses on identifying which enterprise has the power to direct the activities of a variable interest entity that most significantly impacts the variable interest entity's economic performance and (1) the obligation to absorb losses of the variable interest entity or (2) the right to receive benefits from the variable interest entity. As a result of adopting this new accounting standard, we were required to change the way we account for our variable interest in Regulus. Since we and Alnylam Pharmaceuticals, Inc. share the ability to impact Regulus' economic performance, we are no longer the primary beneficiary of Regulus. We adopted the new standard on a prospective basis, therefore beginning in the first quarter of 2010, we deconsolidated Regulus from our condensed consolidated financial statements and began to account for our ownership interest in Regulus using the equity method of accounting. This means that we no longer include Regulus' revenue and operating expenses in our operating results. Instead we include our share of Regulus' operating results on a separate line in our condensed consolidated statement of operations called "Equity in net loss of Regulus Therapeutics Inc." On our condensed consolidated balance sheet, we present our investment in Regulus on a separate line in the non-current liabilities section called "Investment in Regulus Therapeutics Inc." We have not reclassified amounts in the prior period financial statements to conform to the current period presentation. For additional information, see Note 3, *Investment in Regulus Therapeutics Inc.*

Use of estimates

The preparation of condensed consolidated financial statements in conformity with accounting principles generally accepted in the United States requires management to make estimates and assumptions that affect the amounts reported in the condensed consolidated financial statements and

accompanying notes. Actual results could differ from those estimates. Historically, our estimates have been accurate as we have not experienced any material differences between our estimates and our actual results.

Basic and diluted net income (loss) per share

We compute basic net income (loss) per share by dividing the net income (loss) by the weighted-average number of common shares outstanding during the period. As we incurred a loss from continuing operations for the quarters ended March 31, 2010 and 2009, we did not include the following diluted common equivalent shares in the computation of diluted net loss from continuing operations per share because the effect would be anti-dilutive:

- 2 5/8% convertible subordinated notes;
- GlaxoSmithKline convertible promissory notes;
- Dilutive stock options; and
- Warrants issued to Symphony GenIsis Holdings LLC

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Consolidation of variable interest entities

We identify entities as variable interest entities either: (1) that do not have sufficient equity investment at risk to permit the entity to finance its activities without additional subordinated financial support, or (2) in which the equity investors lack an essential characteristic of a controlling financial interest. As of March 31, 2010, we had collaborative arrangements with eight entities that we consider to be variable interest entities. We are not the primary beneficiary for any of these entities. For the three months ended March 31, 2009, our condensed consolidated financial statements included one variable interest entity, Regulus, for which we were the primary beneficiary. As a result of adopting the new accounting standard related to our investment in Regulus in the first quarter of 2010, we deconsolidated Regulus because we are no longer the primary beneficiary of Regulus. See Note 3, *Investment in Regulus Therapeutics Inc.*, for additional details.

Comprehensive income (loss)

SFAS 130, *Reporting Comprehensive Income*, requires us to report, in addition to net income (loss), comprehensive income (loss) and its components. A summary follows (in thousands):

	Three Months Ended March 31,	
	2010	2009
Comprehensive income (loss):		
Unrealized holding gains (losses)	$ 151	$ (510)
Reclassification adjustment for realized loss included in net loss	(925)	—
Net income (loss)	(9,658)	186,218
Comprehensive income (loss)	$ (10,432)	$ 185,708

Convertible debt

We account for our 2 5/8% convertible notes by separating the liability and equity components of the instruments in a manner that reflects our nonconvertible debt borrowing rate when we recognize interest expense in subsequent periods. As a result, we assigned a value to the debt component of our 2 5/8% convertible notes equal to the estimated fair value of a similar debt instrument without the conversion feature, which resulted in us recording the debt at a discount. We are amortizing the resulting debt discount over the life of the debt as additional non-cash interest expense. At March 31, 2010, the principal and accrued interest payable on our 2 5/8% convertible notes was $162.5 million and $545,000, respectively, and the fair value using quoted market prices was $168.8 million. At December 31, 2009, the principal and accrued interest payable on the notes was $162.5 million and $1.6 million, respectively, and the fair value using quoted market prices was $165.8 million.

Stock-based compensation expense

We account for our stock-based compensation expense related to employee stock options and employee stock purchases by estimating the fair value of each employee stock option grant and the employee stock purchase plan (“ESPP”) purchase rights on the date of grant using the Black-Scholes model. The expected term of stock options granted represents the period of time that they are expected to be outstanding. We estimated the expected term of options granted based on historical exercise patterns.

For the three months ended March 31, 2010 and 2009, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Three Months Ended March 31,	
	2010	2009
Risk-free interest rate	2.8%	1.8%
Dividend yield	0.0%	0.0%
Volatility	55.7%	57.0%
Expected Life	5.1 years	4.9 years

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ESPP:

	Three Months Ended March 31,	
	2010	2009
Risk-free interest rate	0.2%	0.3%
Dividend yield	0.0%	0.0%
Volatility	54.8%	70.4%
Expected Life	6 months	6 months

Stock-based compensation expense (in thousands, except per share data) was allocated as follows:

	Three Months Ended March 31,	
	2010	2009
Research and development	$ 2,826	$ 2,260
General and administrative	530	443
Non-cash compensation expense related to stock options included in continuing operations	3,356	2,703
Non-cash compensation expense related to stock options included in equity in net loss of Regulus Therapeutics Inc.	162	—
Non-cash compensation benefit related to stock options included in discontinued operations	—	(1,558)
Total	$ 3,518	$ 1,145
Basic and diluted stock-based compensation expense, per share:		
Net loss per share included in continuing operations	$ (0.03)	$ (0.03)
Net loss per share related to stock options included in equity in net loss of Regulus Therapeutics Inc.	(0.01)	—
Net income per share included in discontinued operations	—	0.02
Total	$ (0.04)	$ (0.01)

As part of our Regulus joint venture, both we and Alnylam issued our own company's stock options to members of Regulus' Board of Directors, Scientific Advisory Board and employees of Regulus. In January 2009 as part of Regulus' conversion to a C-Corporation both we and Alnylam modified our own company's stock options issued to Regulus' employees, members of Regulus' Board of Directors and Scientific Advisory Board to stop vesting in these stock awards before the awards were fully vested. Additionally, in February 2009, Regulus issued options to purchase its own common stock to Regulus' employees, members of Regulus' Board of Directors and members of Regulus' Scientific Advisory Board.

As of March 31, 2010, total unrecognized compensation cost related to non-vested stock-based compensation plans was $16.2 million. We will adjust total unrecognized compensation cost for future changes in estimated forfeitures. We expect to recognize this cost over a weighted average period of 1.4 years.

Impact of recently issued accounting standards

In October 2009, the FASB issued a new accounting standard for revenue arrangements with multiple deliverables. This new standard requires companies to separate multiple-deliverable arrangements and at inception allocate arrangement consideration using a selling price hierarchy. The new standard also requires additional disclosures about multiple-deliverable arrangements. This guidance is effective prospectively for revenue arrangements entered into or materially modified in fiscal years beginning on or after June 15, 2010 and is effective for our fiscal year 2011. We do not expect this new standard to have a material impact on our financial statements.

In March 2010, the FASB issued a new accounting standard that establishes a revenue recognition method for milestone payments in research and development agreements. Under the new standard, entities can make an accounting policy election to recognize a payment that is contingent upon the achievement of a substantive milestone in its entirety in the period in which the milestone is achieved. We have historically applied a revenue recognition method for milestone payments that is consistent with this new standard. Therefore when we adopt this new standard in 2011, the only change required is to provide additional information about the substantive nature of the milestones in our research and development agreements.

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3. Investment in Regulus Therapeutics Inc.

In September 2007, we and Alnylam established Regulus as a company focused on the discovery, development, and commercialization of microRNA-based therapeutics. Regulus combines the strengths and assets of our and Alnylam's technologies, know-how, and intellectual property relating to microRNA-based therapeutics.

We and Alnylam each granted Regulus exclusive licenses to our respective intellectual property for microRNA therapeutic applications, as well as certain early fundamental patents in the microRNA field, including the "Tuschl III", "Sarnow" and "Esau" patent series. Alnylam made an initial investment of $10 million in Regulus to balance venture ownership. We own 51 percent of Regulus and Alnylam owns the remaining 49 percent. Regulus operates as an independent company with a separate board of directors, scientific advisory board and management team. We and Alnylam retain rights to develop and commercialize on pre-negotiated terms microRNA therapeutic products that Regulus decides not to develop either itself or with a partner.

We and Alnylam provide Regulus research and development and general and administrative services under the terms of a services agreement.

In January 2009, Regulus completed a legal reorganization from a limited liability company to a C-Corporation. In March 2009, Regulus raised $20 million in a Series A preferred equity financing, in which we and Alnylam were the sole and equal investors.

In April 2008, Regulus entered into a strategic alliance with GlaxoSmithKline, or GSK, to discover, develop and commercialize novel microRNA-targeted therapeutics to treat inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. The alliance utilizes Regulus' expertise and intellectual property position in the discovery and development of microRNA-targeted therapeutics and provides GSK with an option to license drug candidates directed at four different microRNA targets with relevance in inflammatory disease. Regulus will be responsible for the discovery and development of the microRNA antagonists through completion of clinical proof of concept, unless GSK chooses to exercise its option earlier. After exercise of the option, GSK will have an exclusive license to drugs Regulus develops under each program for the relevant microRNA target for further development and commercialization on a worldwide basis. Regulus will have the right to further develop and commercialize any microRNA therapeutics which GSK chooses not to develop or commercialize.

In 2008, Regulus received $20 million in upfront payments from GSK, including a $15 million option fee and a $5 million note. The note plus interest will convert into Regulus stock in the future if Regulus achieves a minimum level of financing with institutional investors. In addition, we and Alnylam are guarantors of the note, and if the note does not convert or if Regulus does not repay the note in cash by April 2011, we, Alnylam and Regulus may elect to repay the note plus interest with shares of each company's common stock or cash. Regulus is eligible to receive from GSK up to $144.5 million in development, regulatory and sales milestone payments for each of the four microRNA-targeted drugs discovered and developed as part of the alliance. In May 2009, Regulus received a $500,000 discovery milestone payment from its collaboration with GSK for demonstrating a pharmacological effect in immune cells by specific microRNA inhibition. In addition, Regulus would receive from GSK tiered royalties up to double digits on worldwide sales of drugs resulting from the alliance.

In February 2010, Regulus announced the establishment of a new worldwide strategic alliance with GSK to develop and commercialize microRNA therapeutics targeting microRNA 122, or miR-122, for the treatment of hepatitis C virus, or HCV, infection. The new HCV alliance expands the ongoing GSK-Regulus immuno-inflammatory disease alliance formed in 2008. Under the terms of this HCV collaboration, Regulus received $8 million from GSK, including a $3 million license fee and a second $5 million note (guaranteed by Isis and Alnylam) that will convert into Regulus stock in the future if Regulus achieves a minimum level of financing with institutional investors. In addition, Regulus is eligible to receive several near-term significant payments associated with the advancement of an HCV drug, plus additional milestone payments with the potential to earn more than $150 million in miR-122-related combined payments and double-digit royalties consistent with the existing immuno-inflammatory diseases alliance terms established in April 2008. Because GSK has selected Regulus' miR-122 for the new collaboration, the number of immuno-inflammatory programs GSK has an option to license under the 2008 immuno-inflammatory alliance has been reduced from four to three.

As part of the HCV collaboration, Regulus granted GSK a limited license to develop and commercialize the miR-122 antagonist SPC 3649, if GSK acquires rights to this compound. Regulus will receive development and regulatory milestones as well as royalties if GSK develops and commercializes SPC 3649.

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On January 1, 2010, as a result of adopting the new accounting standard for identifying which enterprise has the power to direct activities of a variable interest entity, we prospectively changed the way we account for our variable interest in Regulus. Since we and Alnylam share the ability to impact Regulus' economic performance, we are no longer the primary beneficiary of Regulus. Beginning in the first quarter of 2010, we deconsolidated Regulus from our condensed consolidated financial statements and began to account for our ownership interest in Regulus using the equity method of accounting. Below is a table summarizing the accounting impact to our balance sheet as of January 1, 2010 as a result of adopting the equity method of accounting (in thousands):

	As Originally Reported	As Adjusted	Effect of Change
Total Assets	$ 657,184	$ 626,006	$ (31,178)
Total Liabilities	$ (355,121)	$ (335,524)	$ 19,597
Total Stockholders' Equity	$ (302,063)	$ (290,482)	$ 11,581

Under the equity method of accounting, we were required to suspend losses if our share of Regulus' net loss exceeds the amount of funding we were required to provide. Since we and Alnylam are guarantors of both of the convertible notes that Regulus issued to GSK, we continued to recognize losses in excess of our net investment in Regulus up to the $5 million we guaranteed. If we had been applying the equity method from inception, we would have suspended recognizing our share of Regulus' losses in 2008 because it would have exceeded the amount we guaranteed under the first GSK convertible note. When we made the $10 million investment in March 2009 we would have recognized all of the suspended losses.

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4. Discontinued Operations

In January 2009, AMI completed its acquisition of Ibis for a total purchase price of $215 million. Since we sold Ibis to AMI and Ibis met the criteria for a component of an entity, we reflect Ibis as a discontinued operation. Accordingly, we have presented the operating results of Ibis in our condensed consolidated statements of operations as discontinued operations. Net income from discontinued operations for the first three months of 2009 primarily consisted of the $202.5 million gain related to the sale of Ibis to AMI less $15.5 million of income tax expense. The components of discontinued operations for the three months ended March 31, 2009 are as follows (in thousands):

Revenue	$ —
Total operating expenses	35
Loss from operations	(35)
Loss attributed to noncontrolling interest in Ibis Biosciences, Inc.	6

Loss from discontinued operations	(29)
Gain on sale of Ibis Biosciences, Inc., net of tax	187,025
Net income from discontinued operations, net of tax	$ 186,996

We do not have any remaining assets and liabilities from discontinued operations in our accompanying condensed consolidated balance sheets at March 31, 2010 and December 31, 2009. We have not separately classified cash flows from discontinued operations in our condensed consolidated statement of cash flows.

5. Investments

As of March 31, 2010, our excess cash was primarily invested in commercial paper and debt instruments with strong credit ratings of financial institutions, corporations, U.S. government agencies and the U.S. Treasury. We have established guidelines relative to diversification and maturities that maintain safety and liquidity. We periodically review and modify these guidelines to maximize trends in yields and interest rates without compromising safety and liquidity.

The following table summarizes the contract maturity of the available-for-sale securities we held as of March 31, 2010:

One year or less	61%
After one year but within five years	39%
Total	100%

At March 31, 2010, we had an ownership interest of less than 20% in each of five private companies and two public companies with which we conduct business. The companies are Santaris Pharma A/S, Achaogen, Inc., Atlantic Pharmaceuticals Limited, Altair Therapeutics Inc. and Excaliard, which are privately-held and ATL and iCo Therapeutics Inc., which are publicly-traded. We account for securities in the privately-held companies under the cost method of accounting. During the first three months of 2010, we recognized a $1.0 million loss on investments primarily consisting of an $880,000 non-cash loss related to the other-than-temporary impairment of our equity investment in ATL and a $149,000 valuation allowance we recorded related to our investment in Excaliard. Because realization of our Excaliard investment is uncertain we recorded a full valuation allowance.

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Beginning in the first quarter of 2010, we deconsolidated Regulus from our condensed consolidated financial statements and began to account for our ownership interest in Regulus using the equity method of accounting. As a result, our investment balance at March 31, 2010 did not include Regulus' short-term investments, compared to $14.5 million at December 31, 2009. The following is a summary of our investments (in thousands):

March 31, 2010	Amortized Cost	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Short-term investments:					
Corporate debt securities	$ 91,990	$ 226	$ (38)	$ —	$ 92,178
Debt securities issued by U.S. government agencies	119,976	84	(29)	—	120,031
Debt securities issued by the U.S. Treasury	45,127	63	—	—	45,190
Debt securities issued by states of the United States and political subdivisions of the states	275	—	(4)	—	271
Total securities with a maturity of one year or less	257,368	373	(71)	—	257,670
Corporate debt securities	59,256	181	(83)	—	59,354
Debt securities issued by U.S. government agencies	88,369	50	(23)	—	88,396
Debt securities issued by U.S. Treasury	15,062	47	—	—	15,109
Total securities with a maturity of more than one year	162,687	278	(106)	—	162,859
Subtotal	$ 420,055	$ 651	$ (177)	$ —	$ 420,529
Equity securities:					
Current portion (included in Other current assets)	$ 1,538	$ 1,710	$ —	$ (880)	$ 2,368
Long-term portion (included in Deposits and other assets)	625	—	—	—	625
Subtotal	$ 2,163	$ 1,710	$ —	$ (880)	$ 2,993
	$ 422,218	$ 2,361	$ (177)	$ (880)	$ 423,522

December 31, 2009	Amortized Cost	Unrealized Gains	Unrealized Losses	Estimated Fair Value
Short-term investments:				
Corporate debt securities	$ 102,598	$ 174	$ (34)	$ 102,738
Debt securities issued by U.S. government agencies	151,008	178	(17)	151,169
Debt securities issued by the U.S. Treasury	32,027	42	(10)	32,059
Debt securities issued by states of the United States and political subdivisions of the states	275	—	—	275
Total securities with a maturity of one year or less	285,908	394	(61)	286,241
Corporate debt securities	41,388	262	(103)	41,547
Debt securities issued by U.S. government agencies	110,313	65	(218)	110,160
Debt securities issued by U.S. Treasury	31,136	2	(29)	31,109
Total securities with a maturity of more than one year	182,837	329	(350)	182,816
Subtotal	$ 468,745	$ 723	$ (411)	$ 469,057
Equity securities:				
Current portion (included in Other current assets)	$ 1,229	$ 2,645	$ —	$ 3,874
Long-term portion (included in Deposits and other assets)	625	—	—	625

Subtotal	$ 1,854	$ 2,645	$ —	$ 4,499
	$ 470,599	$ 3,368	$ (411)	$ 473,556

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Investments we consider to be temporarily impaired at March 31, 2010 are as follows (in thousands):

		Less than 12 months of temporary impairment	
	Number of Investments	Estimated Fair Value	Unrealized Losses
Corporate debt securities	57	$ 58,084	$ (121)
Debt securities issued by U.S. government agencies	24	80,596	(51)
Debt securities issued by states of the United States and political subdivisions of the states	1	271	(4)
Total temporarily impaired securities	82	$ 138,951	$ (176)

We believe that the decline in value of these securities is temporary and primarily related to the change in market interest rates since purchase. We believe it is more likely than not that we will be able to hold these securities to maturity. Therefore we anticipate full recovery of their amortized cost basis at maturity.

6. Fair Value Measurements

We use a three-tier fair value hierarchy to prioritize the inputs used in our fair value measurements. These tiers include: Level 1, defined as observable inputs such as quoted prices in active markets, which includes our money market funds and treasury securities classified as available-for-sale securities and equity securities in publicly-held biotechnology companies; Level 2, defined as inputs other than quoted prices in active markets that are either directly or indirectly observable, which includes our fixed income securities and commercial paper classified as available-for-sale securities; and Level 3, defined as unobservable inputs in which little or no market data exists, therefore requiring an entity to develop its own assumptions. To estimate the fair value of securities classified as Level 2, we utilize the services of various fixed income pricing providers that use an industry standard valuation model, which is based on a market approach. The significant inputs for the valuation model include reported trades, broker/dealer quotes, benchmark securities and bids.

Below is a table of the assets that we measure at fair value on a recurring basis. For the following major security types, we break down the inputs used to measure fair value at March 31, 2010 (in thousands):

	Total	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 84,510	$ 84,510	$ —	$ —
Corporate debt securities (2)	151,532	—	151,532	—
Debt securities issued by U.S. government agencies (2)	208,428	—	208,428	—
Debt securities issued by the U.S. Treasury (2)	60,298	60,298	—	—
Debt securities issued by states of the United States and political subdivisions of the states (2)	271	—	271	—
Equity securities (3)	2,368	2,368	—	—
Total	$ 507,407	$ 147,176	$ 360,231	$ —

(1) Included in cash and cash equivalents on our condensed consolidated balance sheet.

(2) Included in short-term investments on our condensed consolidated balance sheet.

(3) Included in other current assets on our condensed consolidated balance sheet.

7. Lease Agreements

We currently occupy approximately 138,500 square feet of laboratory and office space, including a 28,704 square foot facility, which houses our manufacturing suites for our drug development business built to meet Good Manufacturing Practices. We are located in four buildings in Carlsbad, California. We lease all of these buildings under lease agreements. The leases on the three buildings we primarily use for laboratory and office space for our drug development business expire at the end of 2011.

On March 30, 2010 we entered a new lease agreement with an affiliate of BioMed Realty, L.P. Under the lease, BioMed will construct a new 176,000 square foot research facility in Carlsbad, California. Upon completion of construction, we will lease the new facility for a 20-year term and consolidate the majority of our operations in the new facility. The lease has an initial term of 20 years with an option to extend the lease for up to four five-year periods.

Our rent under the new lease is based on a percentage of the total construction costs spent by BioMed to acquire the land and build the new facility. We will begin paying rent on January 1, 2012. Once the new facility is complete, we will be responsible for the costs associated with owning and maintaining the facility. Since our rent is based on a percentage of total construction costs spent by BioMed to acquire the land and build the new facility, and the facility is not yet built, it is

difficult for us to calculate our future payment obligations under the lease. However, as of March 31, 2010, we estimate that the maximum potential future payments we may be required to make over the 20 year term of the lease are $172 million.

Under the lease we have an option to purchase the facility at the end of the fifth, sixth, seventh, eighth, ninth, fifteenth and twentieth year of the lease. The purchase price for the purchase options ending on the fifth through ninth year will be set based on the total construction costs spent by BioMed to acquire the land and build the new facility less rent payments made through the purchase date. The purchase price for the purchase options ending on the fifteenth and twentieth year will be based on fair market value at those times.

In conjunction with the new lease agreement with BioMed, we purchased a parcel of land for $10.1 million and subsequently sold it to BioMed, who will construct the new facility on it. Since we have the option to purchase the facility, including the land, we have continuing involvement in the land which requires us to account for the purchase and sale of the land as a financing transaction. As such, our fixed assets at March 31, 2010 included the land. Additionally, we have recorded a corresponding amount in our non-current liabilities as a long-term financing obligation. Since land is not a depreciable asset, the value of the land and financing obligation we recorded will not change until we exercise our purchase option or the lease is terminated.

We also lease from BioMed an approximately 28,700 square foot facility that houses our manufacturing suites for our drug development business. On March 30, 2010 we amended the lease to extend the term through December 31, 2031, subject to four five-year options to extend the lease, and to obtain an option to purchase the manufacturing facility on similar terms as the purchase options described above.

8. Income Taxes

At December 31, 2009, our balance sheet included an income taxes payable of $7.3 million. As of March 31, 2010 our balance sheet included an income tax receivable of $517,000. This change relates to $7.7 million of income tax payments made to various taxing authorities during the first quarter of 2010 for our 2009 estimated tax liability. The income tax receivable represents the potential amount that could be refunded to us when we file our state and federal income tax returns later this year.

9. Collaborative Arrangements and Licensing Agreements

The information discussed below represents significant partnerships we entered into during 2010. There are no other material changes from the information provided in Note 7—*Collaborative Arrangements and Licensing Agreements* of the Consolidated Financial Statements section, included in our Annual Report on Form 10-K for the year ended December 31, 2009.

Traditional Pharmaceutical Alliances and Licensing

GlaxoSmithKline

In March 2010, we entered into a new strategic alliance with GSK that will apply our antisense drug discovery platform to seek out and develop new therapeutics against targets for rare and serious disease, including infectious diseases and some conditions causing blindness.

Under the terms of the agreement, which covers up to six programs, we received an upfront $35 million payment from GSK and beginning in April 2010, we will amortize this amount over the five year period of our performance based on the research plan included in the agreement. As of March 31, 2010, we have not recognized any revenue related to the $35 million upfront payment from GSK. We are also eligible to receive on average up to $20 million in milestone payments per program up to Phase 2 proof-of-concept. GSK will have the option to license compounds at Phase 2 proof-of-concept, and will be responsible for all further development and commercialization. We will be eligible to receive license fees and milestone payments, totaling up to nearly $1.5 billion, in the event all six programs are successfully developed for one or more indications and commercialized through to pre-agreed sales targets. In addition, we will receive up to double-digit royalties on sales from any product that is successfully commercialized.

10. Segment Information and Concentration of Business Risk

Segment information

We currently report our financial results in two segments, Drug Discovery and Development and Regulus. Segment income (loss) from operations includes revenue less research and development expenses and general and administrative expenses attributable to each segment. See the Business Segments discussion within the "Management's Discussion and Analysis of Financial Condition and Results of Operations" in Item 2 below for additional information on the segments.

Our Drug Discovery and Development segment generates revenue from collaborations with corporate partners and from licensing proprietary patent rights. Revenue from collaborations with corporate partners may consist of upfront payments, funding for research and development activities, milestone payments and royalties or profit sharing payments. This segment's proprietary technology to discover and characterize novel antisense inhibitors has enabled our scientists to modify the properties of our antisense drugs for optimal use with particular targets and thus, to produce a broad proprietary portfolio of drugs applicable to many disease targets.

Our Regulus segment generates revenue from research grants and collaborations with corporate partners such as its strategic alliance with GSK.

The following is information for revenue, loss from operations and total assets by segment (in thousands):

	Isis Drug Discovery and Development	Regulus
Three Months Ended March 31, 2010		
Revenue:		

Research and development	$ 28,556	$ 686
Licensing and royalty	1,370	—
Total segment revenue	$ 29,926	$ 686
Loss from operations	$ (4,880)	$ (3,068)
Total assets as of March 31, 2010	$ 599,723	$ 37,050

As a result of adopting the new accounting standard related to our investment in Regulus, we deconsolidated Regulus from our condensed consolidated financial statements and began to account for ownership interest in Regulus using the equity method of accounting. Therefore in the first quarter of 2010 we began presenting our net share of Regulus' operating results on a separate line in our statement of operations called "Equity in net loss of Regulus Therapeutics Inc." for the three months ended March 31, 2010.

	Drug Discovery and Development	Regulus	Consolidated Total
Three Months Ended March 31, 2009			
Revenue:			
Research and development	$ 29,047	$ 638	$ 29,685
Licensing and royalty	1,891	—	1,891
Total segment revenue	$ 30,938	$ 638	$ 31,576
Income (loss) from operations	$ 1,223	$ (1,865)	$ (642)
Total assets as of December 31, 2009	$ 634,820	$ 22,364	$ 657,184

Concentrations of business risk

We have historically funded our operations from collaborations with corporate partners and a relatively small number of partners have accounted for a significant percentage of our revenue. Revenue from significant partners, which is defined as 10% or more of our total revenue, was as follows:

	Three Months Ended March 31,	
	2010	2009
Partner A	56%	53%
Partner B	33%	8%
Partner C	0%	22%

Contract receivables from three significant partners comprised approximately 55%, 18% and 13% of contract receivables at March 31, 2010. Contract receivables from one significant partner comprised approximately 92% of contract receivables at December 31, 2009.

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ITEM 2. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

In this Report on Form 10-Q, unless the context requires otherwise, "Isis," "Company," "we," "our," and "us," means Isis Pharmaceuticals, Inc. and its subsidiaries.

Forward-Looking Statements

In addition to historical information contained in this Report on Form 10-Q, this Report includes forward-looking statements regarding our business, the therapeutic and commercial potential of our technologies and products in development, and the financial position of Isis Pharmaceuticals, Inc. and Regulus Therapeutics, our majority-owned subsidiary. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward looking statements. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning our programs are described in additional detail in our Annual Report on Form 10-K for the year ended December 31, 2009, which is on file with the U.S. Securities and Exchange Commission, and those identified within this Item entitled "Risk Factors" beginning on page 27 of this Report.

Overview

We are the leading company in antisense technology, exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs. Antisense technology is a direct route from genomics to drugs. With our highly efficient and prolific drug discovery platform we can expand our drug pipeline and our partners' pipelines with antisense drugs that address significant unmet medical needs. Our business strategy is to do what we do best—to discover unique antisense drugs and develop these drugs to key value inflection points. In this way, our organization remains small and focused. We discover new drugs, outlicense our drugs to partners and build a broad base of license fees, milestone payments and royalty income. We maximize the value of the drugs we discover by putting them in the hands of quality partners with late-stage development and commercialization expertise. For example, we partner our drugs with leading pharmaceutical companies with late-stage development, commercialization and marketing expertise, such as Bristol-Myers Squibb, Genzyme, GSK and Eli Lilly and Company. Additionally, we have created a consortium of smaller companies that can broadly exploit the technology with their expertise in specific disease areas. We call these smaller companies our satellite companies. In addition to our cutting edge antisense programs, we maintain technology leadership beyond our core areas of focus through collaborations with Alnylam and Regulus, a company we established and jointly own focused on microRNA therapeutics. We also exploit our inventions with other therapeutic opportunities through collaborations with Achaogen and Archemix Corp. Beyond human therapeutics, we benefit from the commercialization of products of our inventions by other companies that are

better positioned to maximize the commercial potential of these inventions, such as Ibis, a subsidiary of ours that we sold in early 2009 to AMI. All of these aspects fit into our unique business model and create continued shareholder value.

We protect our proprietary RNA-based technologies and products through our substantial patent estate. We remain one of the most prolific patent holders in the United States, ranked as having one of the highest ratios of issued patents per employee with more than 1,600 issued patents. With our ongoing research and development, our patent portfolio continues to grow. The patents not only protect our key assets—our technology and our drugs—they also form the basis for lucrative licensing and partnering arrangements. To date, we have generated more than $390 million from our intellectual property sale and licensing program that helps support our internal drug discovery and development programs.

The clinical success of mipomersen, the lead drug in our cardiovascular franchise, is a clear example of the power of our RNA-based technology. Our clinical experience with mipomersen demonstrates that antisense drugs work in man. We and Genzyme reported positive data from two Phase 3 studies in patients with FH. Both studies met their primary and secondary endpoints with reductions in LDL-C and other generally accepted risk factors for cardiovascular disease. These data are consistent with our observations of mipomersen in earlier clinical studies and support the profile of the drug as a novel treatment to reduce LDL-C in patients with high cholesterol, and at high cardiovascular risk and who cannot reduce their LDL-C sufficiently with currently available lipid-lowering therapies.

With mipomersen we have additional evidence, as we have shown with other antisense drugs, that we can predict the activity of our drugs in man from the preclinical successes we observe in animals. We believe mipomersen's success has validated our technology platform and increased the value of our drugs.

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Since 2007, our partnerships, including our recent strategic alliance with GSK, have generated an aggregate of more than $780 million in payments from licensing fees, equity purchase payments and milestone payments. In addition, for our partnered drugs we have the potential to earn approximately $2.5 billion in future milestone payments. We also will share in the future commercial success of our inventions and drugs resulting from these partnerships through earn out, profit sharing, and/or royalty arrangements. Our strong financial position is a result of the persistent execution of our business strategy and our inventive and focused research and development capabilities.

Business Segments

We currently focus our business on two principal segments:

Drug Discovery and Development Within our primary business segment, we are exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs for us and our partners. With our proprietary drug discovery platform we can rapidly identify drugs, providing a wealth of potential targets to treat a broad range of diseases. We focus our efforts in therapeutic areas where our drugs will work best, efficiently screening many targets in parallel and carefully selecting the best drugs. This efficiency combined with our rational approach to selecting disease targets enables us to build a large and diverse portfolio of drugs designed to treat a variety of health conditions including cardiovascular, metabolic, inflammatory, ocular and neurodegenerative diseases, and cancer. We currently have 22 drugs in development. Our partners are licensed to develop, with our support, 12 of these 22 drugs, which substantially reduces our development costs.

Regulus Therapeutics Inc. In September 2007, we and Alnylam established Regulus as a company focused on the discovery, development and commercialization of microRNA therapeutics. Regulus is addressing therapeutic opportunities that arise from alterations in microRNA expression. Since microRNAs may act as master regulators, affecting the expression of multiple genes in a disease pathway, microRNA therapeutics define a new platform for drug discovery and development and microRNAs may also prove to be an attractive new diagnostic tool for disease characterization.

Beginning in the first quarter of 2010, as a result of adopting a new accounting standard, we no longer included Regulus' revenue and operating expenses in our operating results and no longer included Regulus' cash in our cash balance. See Note 2, *Significant Accounting Policies*, and Note 3, *Investment in Regulus Therapeutics Inc.*, in the Notes to the condensed consolidated financial statements for a more detailed explanation of this change.

Recent Events

Drug Development Highlights

- Mipomersen is being developed by us and Genzyme for patients with high cardiovascular risk who cannot adequately control their cholesterol levels with current therapies and who need new treatment options. We and Genzyme reported positive data from two Phase 3 studies evaluating mipomersen in patients with familial hypercholesterolemia (FH).
  - The full data from a Phase 3 study evaluating mipomersen in patients with homozygous FH were featured and published in The Lancet.
  - In a Phase 3 study evaluating mipomersen in patients with heterozygous FH, we and Genzyme reported that the study met its primary endpoint with a 28% reduction in LDL-C after 26 weeks of treatment compared to an increase of 5% for placebo ($p<0.001$) and also met all of its secondary endpoints. Patients treated with mipomersen had an average LDL-C level of 104 mg/dL at the end of the study and 45% of the mipomersen-treated patients achieved LDL-C levels of less than 100 mg/dL.
- We and our partners initiated clinical studies on 2 drugs including Phase 1 studies on ISIS-SOD1$_{Rx}$ and BMS-PCSK9$_{Rx}$.

Corporate Highlights

- We formed a new strategic alliance worth up to nearly $1.5 billion with GSK to develop antisense drugs to treat rare and infectious diseases
  - We are eligible to receive up to $155 million in pre-licensing payments for all six programs, including the $35 million upfront fee we recently received. We are also eligible to receive up to double-digit royalties on sales from any product that is successfully commercialized.
- We benefitted financially as our partners advanced drugs in development.
  - We received $6 million in a milestone payment from BMS.
- Regulus formed a new alliance with GSK to develop and commercialize microRNA therapeutics targeting miR-122 for hepatitis C viral infection.

Critical Accounting Policies

We prepare our condensed consolidated financial statements in conformity with accounting principles generally accepted in the United States of America. As such, we are required to make certain estimates, judgments and assumptions that we believe are reasonable, based upon the information available to us. These judgments involve making estimates about the effect of matters that are inherently uncertain and may significantly impact our quarterly or annual results of operations and financial condition. Each quarter, our senior management discusses the development, selection and disclosure of such estimates with our audit committee of our board of directors. There are specific risks associated with these critical accounting policies and we caution that future events rarely develop exactly as expected, and that best estimates routinely require adjustment.

Historically, our estimates have been accurate as we have not experienced any material differences between our estimates and our actual results. The significant accounting policies, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results, require the following:

- Assessment of the propriety of revenue recognition and associated deferred revenue;
- Determination of the proper valuation of investments in marketable securities and other equity investments;
- Estimations to assess the recoverability of long-lived assets, including property and equipment, intellectual property and licensed technology;
- Determination of the proper valuation of inventory;
- Determination of the appropriate cost estimates for unbilled preclinical studies and clinical development activities;
- Estimation of our net deferred income tax asset valuation allowance;
- Determination of when we are the primary beneficiary for entities that we identify as variable interest entities;
- Determination of the fair value of convertible debt without the conversion feature; and
- Estimations to determine the fair value of stock-based compensation, including the expected life of the option, the expected stock price volatility over the term of the expected life and estimated forfeitures.

Except as set forth below, there have been no material changes to our critical accounting policies and estimates from the information provided in Item 7, “Management’s Discussion and Analysis of Financial Condition and Results of Operations”, included in our Annual Report on Form 10-K for the year ended December 31, 2009.

Consolidation of variable interest entities

On January 1, 2010, we adopted an accounting standard, which replaced the quantitative-based risks and rewards calculation for determining which enterprise, if any, has a controlling financial interest in a variable interest entity. The new approach focuses on identifying which enterprise has the power to direct the activities of a variable interest entity that most significantly impacts the variable interest entity’s economic performance and (1) the obligation to absorb losses of the variable interest entity or (2) the right to receive benefits from the variable interest entity. As a result of adopting this new accounting standard, we were required to change the way we account for our variable interest in Regulus. Since we and Alnylam Pharmaceuticals, Inc. share the ability to impact Regulus’ economic performance, we are no longer the primary beneficiary of Regulus. We adopted the new standard on a prospective basis, therefore beginning in the first quarter of 2010, we deconsolidated Regulus from our condensed consolidated financial statements and began to account for our ownership interest in Regulus using the equity method of accounting. This means that we no longer include Regulus’ revenue and operating expenses in our operating results. Instead we include our share of Regulus’ operating results on a separate line in our condensed consolidated statement of operations called “Equity in net loss of Regulus Therapeutics Inc.” On our condensed consolidated balance sheet, we presented our investment in Regulus on a separate line in the non-current liabilities section called “Investment in Regulus Therapeutics Inc.” We have not reclassified amounts in the prior period financial statements to conform to the current period presentation. For additional information, see Note 3, Investment in Regulus Therapeutics Inc.

Results of Operations

As a result of adopting the new accounting standard related to our investment in Regulus, we have presented our net share of Regulus’ operating results on a separate line in our statement of operations called “Equity in net loss of Regulus Therapeutics Inc.” for the three months ended March 31, 2010, compared to the line-by-line consolidation for the same period in 2009. We have not reclassified amounts in the prior period financial statements to conform to the current period presentation. We discuss Regulus’ operating results in a separate section below.

As a result of selling Ibis to AMI, Ibis’ financial results are considered discontinued operations. Accordingly, we have presented the operating results of Ibis for 2009 in our financial statements separately as discontinued operations.

Revenue

Total revenue for the three months ended March 31, 2010 was $29.9 million, compared to $31.6 million for the same period in 2009. Our revenue fluctuates based on the nature and timing of payments under agreements with our partners, including license fees, milestone-related payments and other payments. For example, our revenue in the first quarter of 2010 included a $6 million milestone payment that we received from BMS for initiating Phase 1 studies on PCSK9. Although we recognized revenue from the BMS milestone payment in the first quarter of 2010, our revenue compared to the same period in 2009 decreased slightly, primarily because the amortization of the upfront fee from the Ortho-McNeil-Janssen Pharmaceuticals, Inc., or OMJP, collaboration ended in the third quarter of 2009. Revenue also decreased by $638,000 because we are no longer including Regulus’ revenue in our 2010 revenue. In the second quarter of 2010, we will begin amortizing the $35 million upfront payment we received from our recent alliance with GSK into revenue through March 2015.

Collaborations with Alnylam, GSK and Genzyme include ongoing research and development activities. Therefore, we will continue to recognize significant amounts of revenue from these collaborations in the future from the amortization of the upfront fees we received and from research and development funding. Beginning in the second quarter of 2010, our revenue will increase when we start amortizing the $35 million upfront payment we received from GSK. This increase in revenue will be partially offset when the $15 million upfront payment we received from BMS in May 2007 is fully amortized in the second quarter of 2010.

Drug Discovery & Development

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for the three months ended March 31, 2010 was $28.6 million, compared to $29.7 million for the same period in 2009. The decrease was primarily due to the decrease in revenue from our collaboration with OMJP that we describe above offset by the $6 million milestone payment received from BMS. Research and development revenue also decreased by $638,000 because we are no longer including Regulus' revenue in our 2010 revenue.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties for the three months ended March 31, 2010 was $1.4 million, compared to $1.9 million for the same period in 2009. The decrease primarily relates to the sublicensing revenue we earned from Alnylam in the first quarter of 2009 when Alnylam entered into a transaction with Cubist Pharmaceuticals, Inc. that included technology we had licensed to Alnylam.

Operating Expenses

Operating expenses for the three months ended March 31, 2010 were $34.8 million, compared to $32.2 million for the same period in 2009. The higher expenses in 2010 were primarily due to an increase in research and development activities related to the ongoing mipomersen development program and the research activities necessary to achieve our goal of adding three to five new drugs to our pipeline offset by a $2.5 million decrease because we are no longer including Regulus' operating expenses in our 2010 operating expenses.

In order to analyze and compare our results of operations to other similar companies, we believe that it is important to exclude non-cash compensation expense related to stock options from our operating expenses. We believe non-cash compensation expense is not indicative of our operating results or cash flows from our operations. Further, we internally evaluate the performance of our operations excluding it.

Research and Development Expenses

Our research and development expenses consist of costs for antisense drug discovery, antisense drug development, manufacturing and operations and R&D support costs.

The following table sets forth information on research and development costs (in thousands):

	Three Months Ended March 31,	
	2010	2009
Research and development expenses	$ 29,161	$ 26,281
Non-cash compensation expense related to stock options	2,826	2,260
Total research and development	$ 31,987	$ 28,541

For the three months ended March 31, 2010, we incurred total research and development expenses of $29.2 million, compared to $26.3 million for the same period in 2009. The higher expenses in 2010 were primarily due to an increase in research and development activities related to the ongoing mipomersen development program and the research activities necessary to achieve our goal of adding three to five new drugs to our pipeline offset by a $2.2 million decrease because we are no longer including Regulus' research and development expenses in our 2010 operating expenses. All amounts discussed exclude non-cash compensation expense related to stock options.

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Drug Discovery & Development

Antisense Drug Discovery

We use our proprietary antisense technology to generate information about the function of genes and to determine the value of genes as drug discovery targets. We use this information to direct our own antisense drug discovery research, and that of our antisense drug discovery partners. Antisense drug discovery is also the function within Isis that is responsible for advancing antisense core technology.

As we continue to advance our antisense technology, we are investing in our antisense drug discovery programs to expand our and our partners' drug pipeline. We anticipate that our existing relationships and collaborations, as well as prospective new partners, will continue to help fund our research programs, as well as contribute to the advancement of the science by funding core antisense technology research.

Our antisense drug discovery expenses were as follows (in thousands):

	Three Months Ended March 31,	
	2010	2009
Antisense drug discovery	$ 7,746	$ 5,389
Non-cash compensation expense related to stock options	803	698
Total antisense drug discovery	$ 8,549	$ 6,087

Antisense drug discovery costs for the three months ended March 31, 2010 were $7.7 million, compared to $5.4 million for the same periods in 2009, both amounts exclude non-cash compensation expense related to stock options. The higher expenses in 2010 were primarily due to increased activity

levels related to our planned investment to fill our pipeline and additional spending to enhance our platform technology. These activities resulted in an increase in personnel, laboratory supplies and research services provided by third parties in 2010.

Antisense Drug Development

The following table sets forth research and development expenses for our major antisense drug development projects (in thousands):

	Three Months Ended March 31,	
	2010	2009
Mipomersen	$ 6,503	$ 4,758
Other antisense development products	3,865	4,464
Development overhead costs	1,415	1,295
Non-cash compensation expense related to stock options	906	829
Total antisense drug development	$ 12,689	$ 11,346

Antisense drug development expenditures were $11.8 million for the three months ended March 31, 2010, compared to $10.5 million for the same period in 2009, both amounts exclude non-cash compensation expense related to stock options. We attribute the increase primarily to the broad Phase 3 program for mipomersen slightly offset by the decrease in our metabolic disease development projects. Development overhead costs were $1.4 million for the three months ended March 31, 2010 and were slightly higher compared to $1.3 million for the same period in 2009.

We may conduct multiple clinical trials on a drug candidate, including multiple clinical trials for the various indications we may be studying. Furthermore, as we obtain results from trials we may elect to discontinue clinical trials for certain drug candidates in certain indications in order to focus our resources on more promising drug candidates or indications. Our Phase 1 and Phase 2 programs are clinical research programs that fuel our Phase 3 pipeline. When our products are in Phase 1 or Phase 2 clinical trials, they are in a dynamic state where we continually adjust the development strategy for each product. Although we may characterize a product as “in Phase 1” or “in Phase 2,” it does not mean that we are conducting a single, well-defined study with dedicated resources. Instead, we allocate our internal resources on a shared basis across numerous products based on each product’s particular needs at that time. This means we are constantly shifting resources among products. Therefore, what we spend on each product during a particular period is usually a function of what is required to keep the products progressing in clinical development, not what products we think are most important. For example, the number of people required to start a new study is large, the number of people required to keep a study going is modest and the number of people required to finish a study is large. However, such fluctuations are not indicative of a shift in our emphasis from one product to another and cannot be used to accurately predict future costs for each product. And, because we always have numerous products in preclinical and early stage clinical research, the fluctuations in expenses from product to product, in large part, offset one another. If we partner a drug, it may affect the size of a trial, its timing, its total cost and the timing of the related cost. Our partners are developing, with our support, 12 of our 22 drug candidates, which substantially reduces our development costs. As part of our collaboration with Genzyme, we are over time transitioning the

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development responsibility to Genzyme and Genzyme will be responsible for the commercialization of mipomersen. We are contributing up to the first $125 million in funding for the development costs of mipomersen. Thereafter we and Genzyme will share development costs equally. Our initial development funding commitment and the shared funding will end when the program is profitable.

Manufacturing and Operations

Expenditures in our manufacturing and operations function consist primarily of personnel costs, specialized chemicals for oligonucleotide manufacturing, laboratory supplies and outside services. This function is responsible for providing drug supplies to antisense drug discovery and antisense drug development, including the analytical testing to satisfy good laboratory and good manufacturing practices requirements.

Our manufacturing and operations expenses were as follows (in thousands):

	Three Months Ended March 31,	
	2010	2009
Manufacturing and operations	$ 4,133	$ 2,804
Non-cash compensation expense related to stock options	404	325
Total manufacturing and operations	$ 4,537	$ 3,129

Manufacturing and operations expenses for the three months ended March 31, 2010 were $4.1 million, compared to $2.8 million for the same period in 2009, both amounts exclude non-cash compensation expense related to stock options. The increase in expenses was primarily a result of an increase in manufacturing supplies, personnel costs to support our expanded clinical development programs including our broad Phase 3 program for mipomersen and depreciation expense related to the upgrades made to our manufacturing facility.

R&D Support

In our research and development expenses, we include support costs such as rent, repair and maintenance for buildings and equipment, utilities, depreciation of laboratory equipment and facilities, amortization of our intellectual property, information technology costs, procurement costs and waste disposal costs. We call these costs R&D support costs.

The following table sets forth information on R&D support costs (in thousands):

	Three Months Ended March 31,	
	2010	2009
Personnel costs	$ 1,984	$ 1,967

Occupancy	1,542	1,622
Depreciation and amortization	1,239	1,221
Insurance	228	225
Other	505	673
Non-cash compensation expense related to stock options	713	720
Total R&D support costs	$ 6,211	$ 6,428

R&D support costs for the three months ended March 31, 2010 were $5.5 million, compared to $5.7 million for the same period in 2009, both amounts exclude non-cash compensation expense related to stock options. The decrease relates to Regulus' R&D support costs of $293,000 that was included in the three months ended March 31, 2009 which we are no longer including in our 2010 operating expenses.

General and Administrative Expenses

General and administrative expenses include corporate costs required to support our company, our employees and our stockholders. These costs include personnel and outside costs in the areas of legal, human resources, investor relations, and finance. Additionally, we include in general and administrative expenses such costs as rent, repair and maintenance of buildings and equipment, depreciation, utilities, information technology and procurement costs that we need to support the corporate functions listed above.

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The following table sets forth information on general and administrative expenses (in thousands):

	Three Months Ended March 31,	
	2010	2009
General and administrative expenses	$ 2,289	$ 3,234
Non-cash compensation expense related to stock options	530	443
Total general and administrative expenses	$ 2,819	$ 3,677

General and administrative expenses for the three months ended March 31, 2010 were $2.3 million, compared to $3.2 million for the same period in 2009. The decrease primarily relates to Regulus' general and administrative expenses of $657,000 for the three months ended March 31, 2009 which we are no longer including in our 2010 operating expenses. All amounts discussed exclude non-cash compensation expense related to stock options.

Equity in Net Loss of Regulus Therapeutics Inc.

Beginning in the first quarter of 2010, as a result of adopting a new accounting standard, we no longer include Regulus' revenue and operating expenses in our operating results. Instead we are presenting our share of Regulus' operating results on a separate line in our condensed consolidated statement of operations called "Equity in net loss of Regulus Therapeutics Inc." Prior to the adoption of the new accounting standard, we consolidated Regulus' financial results on a line-by-line basis. See Note 2, *Significant Accounting Policies*, and Note 3, *Investment in Regulus Therapeutics Inc.*, in the Notes to the condensed consolidated financial statements for a more detailed explanation of this change.

Our equity in net loss of Regulus for the three months ended March 31, 2010 was $1.5 million. Under the new standard, we had the option to adopt it on a retrospective or prospective basis. We chose to adopt it prospectively therefore we did not adjust our prior period results. If we had retrospectively adopted the new standard, the equity in net loss of Regulus for the first three months of 2009 would have been $2.8 million which would have represented our share of Regulus' loss in the first quarter of 2009 plus $1.7 million in losses which would have been previously suspended. Under the equity method of accounting, we were required to suspend losses if our share of Regulus' net loss exceeds the amount of funding we were required to provide. When we made the $10 million investment in March 2009, we would have recognized all of the suspended losses.

Investment Income

Investment income for the three months ended March 31, 2010 totaled $955,000, compared to $2.1 million for the same period in 2009. The decrease in investment income was primarily due to a lower average return on our investments resulting from the current market conditions and a lower average cash balance.

Interest Expense

Interest expense for the three months ended March 31, 2010 was $3.2 million and was slightly higher compared to $3.1 million for the same period in 2009.

Gain (Loss) on Investments, Net

Loss on investments for the three months ended March 31, 2010 was $1.0 million, compared to a gain on investment of $58,000 for the same period in 2009. The net loss on investments for the first three months of 2010 consists of an $880,000 non-cash loss related to the other-than-temporary impairment of our equity investment in ATL and a $149,000 valuation allowance we recorded related to our investment in Excaliard slightly offset by realized gains on sales of our available-for-sale securities. Because realization of our Excaliard investment is uncertain we recorded a full valuation allowance. The gain on investments for the first three months of 2009 represents gains on sales of our available-for-sale securities.

Income Tax Expense

Even though we finished the first quarter of 2009 with a net loss from continuing operations, we had taxable income, which is primarily a result of the significant upfront payments that we received from our strategic alliance with Genzyme in 2008 and the gain we recognized on the sale of Ibis to AMI in early 2009. We recorded income tax expense in continuing operations of $160,000 for the first three months of 2009 as part of our financial results from continuing operations.

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Net Loss from Continuing Operations attributable to Isis Pharmaceuticals, Inc. Common Stockholders

The following table sets forth computations for our net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders (in thousands):

	Three Months Ended March 31,	
	2010	2009
Net loss from continuing operations, including income tax expense and equity in net loss of Regulus Therapeutics Inc.	$ (9,658)	$ (1,691)
Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	—	913
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (9,658)	$ (778)

Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders for the three months ended March 31, 2010 was $9.7 million, compared to $778,000 for the same period in 2009. The increase in our net loss from continuing operations was primarily due to the following:

- $4.2 million increase in our net operating loss;
- $1.2 million decrease in investment income due to a lower average return on investments resulting from the current market conditions and a lower average cash balance; and
- $880,000 non-cash loss related to the impairment of our equity investment in ATL.

Net Income from Discontinued Operations

Since we sold Ibis to AMI in the first quarter of 2009 and Ibis met the criteria for a component of an entity, we reflected Ibis as a discontinued operation on our financial statements. Accordingly, we have presented the operating results of Ibis in our condensed consolidated statements of operations as discontinued operations. Net income from discontinued operations, net of tax, for the three months ended March 31, 2009 was $187.0 million and primarily consisted of the $202.5 million gain less $15.5 million of income taxes.

Net Income (Loss) and Net Income (Loss) Per Share attributable to Isis Pharmaceuticals, Inc. Common Stockholders

Net loss attributable to Isis Pharmaceuticals, Inc. common stockholders for the three months ended March 31, 2010 was $9.7 million, compared to a net income of $186.2 million for the same period in 2009. Basic and diluted net loss per share for the three months ended March 31, 2010 was $0.10 per share, compared to basic and diluted net income of $1.91 per share for the same period in 2009. Net income and net income per share in 2009 primarily consisted of the $187.0 million gain, net of tax, which we recognized when we sold Ibis to AMI in the first quarter of 2009.

Regulus Therapeutics Segment

Regulus' revenue for the three months ended March 31, 2010 was $686,000 and was slightly higher compared to $638,000 for the same period in 2009.

The following table sets forth information on Regulus' operating expenses (in thousands):

	Three Months Ended March 31,	
	2010	2009
Research and development expenses	$ 2,791	$ 2,156
General and administrative expenses	801	657
Non-cash compensation expense related to stock options	162	(310)
Total Regulus' operating expenses	$ 3,754	$ 2,503

Operating expenses for Regulus were $3.6 million for the three months ended March 31, 2010, compared to $2.8 million for the same period in 2009, both amounts exclude non-cash compensation expense related to stock options. The increase was primarily related to Regulus' continued efforts to build its team to support its internal microRNA programs and the efforts associated with its GSK collaboration, which began in April 2008. With the strategic alliance with GSK, we anticipate that Regulus' expenses will increase going forward as Regulus advances its research and development activities.

Liquidity and Capital Resources

We have financed our operations with revenue primarily from research and development under collaborative agreements. Additionally, we have earned licensing and royalty revenue from the sale or licensing of our intellectual property. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt.

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From our inception through March 31, 2010, we have earned approximately $848.6 million in revenue from contract research and development and the sale and licensing of our intellectual property. From the time we were founded through March 31, 2010, we have raised net proceeds of approximately $817.1 million from the sale of our equity securities and we have borrowed approximately $562.2 million under long-term debt arrangements to finance a portion of our operations.

As of March 31, 2010, we had cash, cash equivalents and short-term investments of $519.1 million and stockholders' equity of $284.4 million. In comparison, we had cash, cash equivalents and short-term investments of $574.3 million and stockholders' equity of $302.1 million at December 31, 2009. At March 31, 2010, we had consolidated working capital of $438.3 million, compared to $484.7 million at December 31, 2009. The decrease in cash and working capital primarily relates to cash used in the first quarter of 2010 for our operations, including a $7.7 million payment that we made for 2009 income taxes, along with a $30.7 million decrease because we are no longer including Regulus' cash in our cash balance. Our cash balance at March 31, 2010 does not include the $35 million upfront payment that we received in April 2010 from our recent preferred partnership with GSK. Including the money from GSK, so far in 2010, we have received more than $55 million from our corporate partnerships.

As of March 31, 2010, our debt and other obligations totaled $135.5 million, compared to $140.8 million at December 31, 2009. The decrease primarily relates to the $5.3 million convertible promissory note and the $949,000 equipment financing arrangement on the books of Regulus as of December 31, 2009 which we are no longer consolidating in our 2010 balance sheet and $963,000 of principal payments we made on our equipment financing arrangement, offset by $1.9 million of non-cash amortization of the debt discount we recorded in the first quarter of 2010 related to our $2^5/_8$ percent convertible notes. We will continue to use equipment lease financing as long as the terms remain commercially attractive.

The following table summarizes our contractual obligations as of March 31, 2010. The table provides a breakdown of when obligations become due. We provide a more detailed description of the major components of our debt in the paragraphs following the table:

	Payments Due by Period (in millions)				
Contractual Obligations (selected balances described below)	**Total**	**Less than 1 year**	**1-3 years**	**3-5 years**	**After 5 years**
$2^5/_8$ percent Convertible Subordinated Notes (principal and interest payable)	$ 179.6	$ 4.3	$ 8.5	$ 166.8	$ —
Equipment Financing Arrangements (principal and interest payable)	$ 8.7	$ 4.4	$ 4.3	$ —	$ —
Other Obligations (principal and interest payable)	$ 1.6	$ 0.1	$ 0.1	$ 0.1	$ 1.3
Operating Leases	$ 32.3	$ 3.1	$ 4.1	$ 2.3	$ 22.8
Total	$ 222.2	$ 11.9	$ 17.0	$ 169.2	$ 24.1

Our contractual obligations consist primarily of our publicly traded convertible debt. In addition, we also have equipment financing arrangements and other obligations.

In January 2007, we completed a $162.5 million convertible debt offering, which raised proceeds of approximately $157.1 million, net of $5.4 million in issuance costs. We included the issuance costs in our balance sheet and are amortizing these costs to interest expense over the life of the debt. The $162.5 million convertible subordinated notes mature in 2027 and bear interest at $2^5/_8$ percent, which is payable semi-annually. The $2^5/_8$ percent notes are convertible, at the option of the note holders, into approximately 11.1 million shares of our common stock at a conversion price of $14.63 per share. We will be able to redeem these notes at a redemption price equal to 100.75 percent of the principal amount between February 15, 2012 and February 14, 2013; 100.375 percent of the principal amount between February 15, 2013 and February 14, 2014; and 100 percent of the principal amount thereafter. Holders of the $2^5/_8$ percent notes may also require us to repurchase the $2^5/_8$ percent notes on February 15, 2014, February 15, 2017 and February 15, 2022, and upon the occurrence of certain defined conditions, at 100 percent of the principal amount of the $2^5/_8$ percent notes being repurchased plus unpaid interest.

In October 2008, we entered into a loan agreement related to an equipment financing and in September 2009, we amended the loan agreement to increase the aggregate maximum amount of principal we can draw under the agreement. Under the loan agreement, we and Regulus could borrow up to $19.4 million in principal to finance the purchase of equipment. The $19.4 million does not include the $600,000 Ibis borrowed in October 2008 that was fully repaid in the first quarter of 2009. Each draw down under the loan agreement has a term of three years, with principal and interest payable monthly. We calculate interest on amounts we borrow under the loan agreement based upon the three year interest rate swap at the time we make each draw down plus 4 percent. We are using the equipment purchased under the loan agreement as

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collateral. We have drawn down $13.0 million in principal under this loan agreement at a weighted average interest rate of 6.65 percent. The carrying balance under this loan agreement at March 31, 2010 and December 31, 2009 was $8.1 million and $10.0 million, respectively.

We currently occupy approximately 138,500 square feet of laboratory and office space, including a 28,704 square foot facility, which houses our manufacturing suites for our drug development business built to meet Good Manufacturing Practices. We are located in four buildings in Carlsbad, California. We lease all of these buildings under lease agreements. The leases on the three buildings we primarily use for laboratory and office space for our drug development business expire at the end of 2011.

On March 30, 2010 we entered a new lease agreement with an affiliate of BioMed Realty, L.P. Under the lease, BioMed will construct a new 176,000 square foot research facility in Carlsbad, California. Upon completion of construction, we will lease the new facility for a 20-year term and consolidate the majority of our operations in the new facility. The lease has an initial term of 20 years with an option to extend the lease for up to four five-year periods.

Our rent under the new lease is based on a percentage of the total construction costs spent by BioMed to acquire the land and build the new facility. We will begin paying rent on January 1, 2012. Once the new facility is complete, we will be responsible for the costs associated with owning and maintaining the facility. Since our rent is based on a percentage of total construction costs spent by BioMed to acquire the land and build the new facility, and the facility is not yet built, it is difficult for us to calculate our future payment obligations under the lease. However, as of March 31, 2010, we estimate that the maximum potential future payments we may be required to make over the 20 year term of the lease are $172 million.

We also lease from BioMed an approximately 28,700 square foot facility that houses our manufacturing suites for our drug development business. On March 30, 2010 we amended the lease to extend the term through December 31, 2031, subject to four five-year options to extend the lease, and to obtain an option to purchase the manufacturing facility on similar terms as the purchase options described above.

In addition to contractual obligations, we had outstanding purchase orders as of March 31, 2010 for the purchase of services, capital equipment and materials as part of our normal course of business.

We plan to continue to enter into collaborations with partners to provide for additional revenue to us and we may be required to incur additional cash expenditures related to our obligations under any of the new agreements we may enter into. We currently intend to use our cash and short-term equivalents to finance our activities. However, we may also pursue other financing alternatives, like issuing additional shares of our common stock, issuing debt instruments, refinancing our existing debt, or securing lines of credit. Whether we use our existing capital resources or choose to obtain financing will depend on various factors, including the future success of our business, the prevailing interest rate environment and the condition of financial markets generally.

RISK FACTORS

Investing in our securities involves a high degree of risk. You should consider carefully the following information about the risks described below, together with the other information contained in this report and in our other public filings in evaluating our business. If any of the following risks actually occur, our business could be materially harmed, and our financial condition and results of operations could be materially and adversely affected. As a result, the trading price of our securities could decline, and you might lose all or part of your investment. We have marked with an asterisk those risk factors that reflect substantive changes from the risk factors included in our Annual Report on Form 10-K for the year ended December 31, 2009.

Risks Associated with our Drug Discovery and Development Business

If we or our partners fail to obtain regulatory approval for our drugs, we will not be able to sell them.

We and our partners must conduct time-consuming, extensive and costly clinical trials to show the safety and efficacy of each of our drugs, including mipomersen and ISIS 113715, before a drug can be approved for sale. We must conduct these trials in compliance with FDA regulations and with comparable regulations in other countries. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of our drugs, including mipomersen and ISIS 113715, it will not approve them or will require additional studies, which can be time consuming and expensive and which will delay commercialization of a drug. We and our partners may not be able to obtain necessary regulatory approvals on a timely basis, if at all, for any of our drugs, including mipomersen and ISIS 113715. Failure to receive these approvals or delays in these approvals could prevent or delay commercial introduction of a product, including mipomersen and ISIS 113715, and, as a result, could negatively impact our ability to generate revenue from product sales. In addition, following approval of a drug, we and our partners must comply with comprehensive government regulations regarding how we manufacture, market and distribute drug products. If we fail to comply with these regulations, regulators could force us to withdraw a drug from the market or impose other penalties or requirements that also could have a negative impact on our financial results.

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We have only introduced one commercial drug product, Vitravene. We cannot guarantee that any of our other drugs, including mipomersen and ISIS 113715, will be safe and effective, will be approved for commercialization or that our partners or we can successfully commercialize these drugs.

If the results of clinical testing indicate that any of our drugs under development are not suitable for commercial use we may need to abandon one or more of our drug development programs.

Drug discovery and development has inherent risks and the historical failure rate for drugs is high. Antisense technology in particular is relatively new and unproven. If we cannot demonstrate that our drugs, including mipomersen and ISIS 113715, are safe and effective drugs for human use, we may need to abandon one or more of our drug development programs.

In the past, we have invested in clinical studies of drugs that have not met the primary clinical end points in their Phase 3 studies. In March 2003, we reported the results of a Phase 3 clinical trial of Affinitak in patients with late-stage NSCLC and in October 2004, we reported the results of a second similar Phase 3 clinical trial. In each case, Affinitak failed to demonstrate improved survival sufficient to support a new drug application filing. In December 2004, we reported the results of our Phase 3 clinical trials of alicaforsen in patients with active Crohn's disease, in which alicaforsen did not demonstrate statistically significant induction of clinical remissions compared to placebo. Similar results could occur with the clinical trials for our other drugs, including mipomersen and ISIS 113715. If any of our drugs in clinical studies, including mipomersen and ISIS 113715, do not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for these and other drugs and our stock price could decline.

Even if our drugs are successful in preclinical and early human clinical studies, these results do not guarantee the drugs will be successful in late-stage clinical trials.

Successful results in preclinical or early human clinical trials, including the Phase 2 results for mipomersen and ISIS 113715, may not predict the results of late-stage clinical trials. There are a number of factors that could cause a clinical trial to fail or be delayed, including:

- the clinical trial may produce negative or inconclusive results;
- regulators may require that we hold, suspend or terminate clinical research for noncompliance with regulatory requirements;
- we, our partners, the FDA or foreign regulatory authorities could suspend or terminate a clinical trial due to adverse side effects of a drug on subjects or patients in the trial;
- we may decide, or regulators may require us, to conduct additional preclinical testing or clinical trials;
- enrollment in our clinical trials may be slower than we anticipate;
- the cost of our clinical trials may be greater than we anticipate; and
- the supply or quality of our drugs or other materials necessary to conduct our clinical trials may be insufficient, inadequate or delayed.

Any failure or delay in one of our clinical trials, including our Phase 2 or Phase 3 development programs for mipomersen and ISIS 113715, could reduce the commercial viability of our drugs, including mipomersen and ISIS 113715.

If the market does not accept our products, we are not likely to generate revenues or become consistently profitable.

Our success will depend upon the medical community, patients and third-party payors accepting our products as medically useful, cost-effective and safe. Even if approved for commercialization, doctors may not use our products to treat patients. We currently have one commercially approved drug product, Vitravene, a treatment for CMV, retinitis in AIDS patients, which addresses a small market. Our partners and we may not successfully commercialize additional products.

The degree of market acceptance for any of our products depends upon a number of factors, including:

- the receipt and scope of regulatory approvals;
- the establishment and demonstration in the medical and patient community of the efficacy and safety of our drugs and their potential advantages over competing products;

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- the cost and effectiveness of our drugs compared to other available therapies;
- the patient convenience of the dosing regimen for our drugs; and
- reimbursement policies of government and third-party payors.

Based on the profile of our drugs, physicians, patients, patient advocates, payors or the medical community in general may not accept and use any products that we may develop.

If we cannot manufacture our drug products or contract with a third party to manufacture our drug products at costs that allow us to charge competitive prices to buyers, we will not be able to market products profitably.

If we successfully commercialize any of our drugs, we would be required to establish large-scale commercial manufacturing capabilities either on our own or through a third party manufacturer. In addition, as our drug development pipeline increases and matures, we will have a greater need for clinical trial and commercial manufacturing capacity. We have limited experience manufacturing pharmaceutical products of the chemical class represented by our drugs, called oligonucleotides, on a commercial scale for the systemic administration of a drug. There are a small number of suppliers for certain capital equipment and raw materials that we use to manufacture our drugs, and some of these suppliers will need to increase their scale of production to meet our projected needs for commercial manufacturing. Further, we must continue to improve our manufacturing processes to allow us to reduce our product costs. We may not be able to manufacture at a cost or in quantities necessary to make commercially successful products.

Also, manufacturers, including us, must adhere to the FDA's current Good Manufacturing Practices regulations, which the FDA enforces through its facilities inspection program. We and our contract manufacturers may not be able to comply or maintain compliance with Good Manufacturing Practices regulations. Non-compliance could significantly delay or prevent our receipt of marketing approval for potential products, including mipomersen and ISIS 113715, or result in FDA enforcement action after approval that could limit the commercial success of our potential products, including mipomersen and ISIS 113715.

If our drug discovery and development business fails to compete effectively, our drugs will not contribute significant revenues.

Our competitors are engaged in all areas of drug discovery throughout the world, are numerous, and include, among others, major pharmaceutical companies and specialized biopharmaceutical firms. Other companies are engaged in developing antisense technology. Our competitors may succeed in developing drugs that are:

- priced lower than our drugs;
- safer than our drugs;
- more effective than our drugs; or
- more convenient to use than our drugs.

These competitive developments could make our products obsolete or non-competitive.

Certain of our partners are pursuing other technologies or developing other drugs either on their own or in collaboration with others, including our competitors, to develop treatments for the same diseases targeted by our own collaborative programs. Competition may negatively impact a partner's focus on and commitment to our drugs and, as a result, could delay or otherwise negatively affect the commercialization of our drugs.

Many of our competitors have substantially greater financial, technical and human resources than we do. In addition, many of these competitors have significantly greater experience than we do in conducting preclinical testing and human clinical trials of new pharmaceutical products and in obtaining FDA and other regulatory approvals of products for use in health care. Accordingly, our competitors may succeed in obtaining regulatory approval for products earlier than we do. We will also compete with respect to marketing and sales capabilities, areas in which we have limited or no experience.

Disagreements between Alnylam and us regarding the development of our microRNA technology may cause significant delays and other impediments in the development of this technology, which could negatively affect the value of the technology and our investment in Regulus.

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Regulus is a jointly owned company that we and Alnylam established to focus on the discovery, development, and commercialization of microRNA. As part of this joint venture, we exclusively licensed to Regulus our intellectual property rights covering microRNA. Regulus is operated as an independent company and governed by a board of directors. We and Alnylam can elect an equal number of directors to serve on the Regulus Board. Regulus researches and develops microRNA projects and programs pursuant to an operating plan that its board approves. Any disagreements between Alnylam and us regarding a development decision or any other decision submitted to Regulus' board may cause significant delays in the development and commercialization of our microRNA technology and could negatively affect the value of our investment in Regulus.

We depend on third parties in the conduct of our clinical trials for our drugs and any failure of those parties to fulfill their obligations could adversely affect our development and commercialization plans.

We depend on independent clinical investigators, contract research organizations and other third-party service providers in the conduct of our clinical trials for our drugs and expect to continue to do so in the future. For example, Medpace is the primary clinical research organization for clinical trials for mipomersen. We rely heavily on these parties for successful execution of our clinical trials, but do not control many aspects of their activities. For example, the investigators are not our employees. However, we are responsible for ensuring that these third parties conduct each of our clinical trials in accordance with the general investigational plan and protocols for the trial. Third parties may not complete activities on schedule, or may not conduct our clinical trials in accordance with regulatory requirements or our stated protocols. The failure of these third parties to carry out their obligations or a termination of our relationship with these third parties could delay or prevent the development, approval and commercialization of our drugs, including mipomersen.

Risks Associated with our Businesses as a Whole

We have incurred losses, and our business will suffer if we fail to consistently achieve profitability in the future.*

Because product discovery and development require substantial lead-time and money prior to commercialization, our expenses have generally exceeded our revenue since we were founded in January 1989. As of March 31, 2010, we had an accumulated deficit of approximately $705.1 million and stockholders' equity of approximately $284.4 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from research grants and the sale or licensing of our patents as well as interest income. We currently have only one product, Vitravene, approved for commercial use. This product has limited sales potential, and Novartis, our exclusive distribution partner for this product, no longer markets it. We expect to incur additional operating losses over the next several years, and these losses may increase if we cannot increase or sustain revenue. We may not successfully develop any additional products or services, or achieve or sustain future profitability.

Since corporate partnering is a key part of our strategy to fund the development and commercialization of our development programs, if any of our collaborative partners fail to fund our collaborative programs, or if we cannot obtain additional partners, we may have to delay or stop progress on our product development programs.

To date, corporate partnering has played a key role in our strategy to fund our development programs and to add key development resources. We plan to continue to rely on additional collaborative arrangements to develop and commercialize our products, including ISIS 113715. However, we may not be able to negotiate additional attractive collaborative arrangements.

Our corporate partners are developing and/or funding, many of the drugs in our development pipeline, including Altair, ATL, Atlantic Pharmaceuticals, Bristol-Myers Squibb, iCo, Eli Lilly and Company, OncoGenex, and Teva. In addition, we have a major strategic alliance with Genzyme in which Genzyme will develop and commercialize mipomersen. If any of these pharmaceutical companies stop funding and/or developing these products, our business could suffer and we may not have, or be willing to dedicate, the resources available to develop these products on our own.

Our collaborators can terminate their relationships with us under certain circumstances, some of which are outside of our control. For example, in November 2004 based on the disappointing results of the Phase 3 clinical trials, Eli Lilly and Company discontinued its investment in Affinitak.

In addition, the disappointing results of the two Affinitak clinical trials, our Phase 3 clinical trials of alicaforsen in patients with active Crohn's disease, or any future clinical trials could impair our ability to attract new collaborative partners. If we cannot continue to secure additional collaborative partners, our revenues could decrease and the development of our drugs could suffer.

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Even with funding from corporate partners, if our partners do not effectively perform their obligations under our agreements with them, it would delay or stop the progress of our product development programs.

In addition to receiving funding, we enter into collaborative arrangements with third parties to:

- conduct clinical trials;
- seek and obtain regulatory approvals; and
- manufacture, market and sell existing and future products.

Once we have secured a collaborative arrangement to further develop and commercialize one of our development programs, such as our collaborations with Genzyme and Bristol-Myers Squibb, these collaborations may not continue or result in commercialized drugs, or may not progress as quickly as we anticipated.

For example, a collaborator such as Genzyme or Bristol-Myers Squibb, could determine that it is in its financial interest to:

- pursue alternative technologies or develop alternative products that may be competitive with the product that is part of the collaboration with us;
- pursue higher-priority programs or change the focus of its own development programs; or
- choose to devote fewer resources to our drugs than it does for its own drugs under development.

If any of these occur, it could affect our partner's commitment to the collaboration with us and could delay or otherwise negatively affect the commercialization of our drugs.

If we do not progress in our programs as anticipated, the price of our securities could decrease.

For planning purposes, we estimate and may disclose the timing of a variety of clinical, regulatory and other milestones, such as when we anticipate a certain drug will enter the clinic, when we anticipate completing a clinical trial, or when we anticipate filing an application for marketing approval. We base our estimates on present facts and a variety of assumptions. Many underlying assumptions are outside of our control. If we do not achieve milestones in accordance with our or investors' expectations, the price of our securities would likely decrease.

For example, in April 2008 the FDA provided guidance regarding approval requirements for mipomersen. The FDA indicated that reduction of LDL-C is an acceptable surrogate endpoint for accelerated approval of mipomersen for use in patients with homozygous familial hypercholesterolemia, or hoFH. The FDA will require data from two ongoing preclinical studies for carcinogenicity to be included in the hoFH filing, which is now anticipated to take place in the first half of 2011. The FDA also indicated that for broader indications in high risk, high cholesterol patients an outcome study would be required for approval. This FDA guidance caused us to revise our development plans and timelines and, as a result, to accelerate our planned outcome trial.

If we cannot protect our patents or our other proprietary rights, others may compete more effectively against us.

Our success depends to a significant degree upon our ability to continue to develop and secure intellectual property rights to proprietary products and services. However, we may not receive issued patents on any of our pending patent applications in the United States or in other countries. In addition, the scope of any of our issued patents may not be sufficiently broad to provide us with a competitive advantage. Furthermore, our issued patents or patents licensed to us may be successfully challenged, invalidated or circumvented so that our patent rights would not create an effective competitive barrier or revenue source.

Intellectual property litigation could be expensive and prevent us from pursuing our programs.

It is possible that in the future we may have to defend our intellectual property rights. In the event of an intellectual property dispute, we may be forced to litigate to defend our rights or assert them against others. Disputes could involve arbitration, litigation or proceedings declared by the United States Patent and Trademark Office or the International Trade Commission or foreign patent authorities. Intellectual property litigation can be extremely expensive, and this expense, as well as the consequences should we not prevail, could seriously harm our business.

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For example, in December 2006, the European Patent Office, or EPO, Technical Board of Appeal reinstated with amended claims our Patent EP0618925 which claims a class of antisense compounds, any of which is designed to have a sequence of phosphorothioate-linked nucleotides having two regions of chemically modified RNA flanking a region of DNA. Prior to its reinstatement, this patent was originally opposed by several parties and revoked by an EPO Opposition Division in December of 2003. We intend to fully exercise our rights under this patent by pursuing licensing arrangements, but if licensing efforts are unsuccessful we may choose to assert our rights through litigation.

If a third party claims that our products or technology infringe its patents or other intellectual property rights, we may have to discontinue an important product or product line, alter our products and processes, pay license fees or cease certain activities. We may not be able to obtain a license to needed intellectual property on favorable terms, if at all. There are many patents issued or applied for in the biotechnology industry, and we may not be aware of patents or applications held by others that relate to our business. This is especially true since patent applications in the United States are filed confidentially for the first 18 months. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain unresolved.

If we fail to obtain timely funding, we may need to curtail or abandon some of our programs.*

All of our drugs are undergoing clinical trials or are in the early stages of research and development. All of our drugs under development will require significant additional research, development, preclinical and/or clinical testing, regulatory approval and a commitment of significant additional resources prior to their commercialization. As of March 31, 2010, we had cash, cash equivalents and short-term investments equal to $519.1 million. If we do not meet our goals to commercialize our products, or to license our drugs and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

- changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements;
- continued scientific progress in our research, drug discovery and development programs;
- the size of our programs and progress with preclinical and clinical trials;
- the time and costs involved in obtaining regulatory approvals;
- competing technological and market developments, including the introduction by others of new therapies that address our markets; and
- the profile and launch timing of our drugs.

If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available at all or on acceptable terms. If we raise additional funds by issuing equity securities, the shares of existing stockholders will be diluted and their price, as well as the price of our other securities, may decline. If adequate funds are not available or not available on acceptable terms, we may have to cut back on one or more of our research, drug discovery or development programs. For example, in January 2005 we decided to terminate the development of two lower priority drugs, ISIS 14803 and ISIS 104838. Alternatively, we may obtain funds through arrangements with collaborative partners or others, which could require us to give up rights to certain of our technologies, drugs or products.

The loss of key personnel, or the inability to attract and retain highly skilled personnel, could make it more difficult to run our business and reduce our likelihood of success.

We are dependent on the principal members of our management and scientific staff. We do not have employment agreements with any of our executive officers that would prevent them from leaving us. The loss of our management and key scientific employees might slow the achievement of important research and development goals. It is also critical to our success that we recruit and retain qualified scientific personnel to perform research and development work. We may not be able to attract and retain skilled and experienced scientific personnel on acceptable terms because of intense competition for experienced scientists among many pharmaceutical and health care companies, universities and non-profit research institutions. In addition, failure to succeed in clinical trials may make it more challenging to recruit and retain qualified scientific personnel.

If the price of our securities continues to be highly volatile, this could make it harder for you to liquidate your investment and could increase your risk of suffering a loss.*

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The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding March 31, 2010, the market price of our common stock ranged from $8.59 to $18.81 per share. On May 3, 2010, the closing price of our common stock on The Nasdaq Global Select Market was $10.88. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical trial results, technological innovations or new products being developed by us or our competitors, governmental regulation, regulatory approval, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

Because we use biological materials, hazardous materials, chemicals and radioactive compounds, if we do not comply with laws regulating the protection of the environment and health and human safety, our business could be adversely affected.

Our research, development and manufacturing activities involve the use of potentially harmful biological materials as well as materials, chemicals and various radioactive compounds that could be hazardous to human health and safety or the environment. These materials and various wastes resulting from their use are stored at our facilities in Carlsbad, California pending ultimate use and disposal. We cannot completely eliminate the risk of contamination, which could cause:

- interruption of our research, development and manufacturing efforts;
- injury to our employees and others;
- environmental damage resulting in costly clean up; and
- liabilities under federal, state and local laws and regulations governing health and human safety, as well as the use, storage, handling and disposal of these materials and resultant waste products.

In such an event, we may be held liable for any resulting damages, and any liability could exceed our resources. Although we carry insurance in amounts and type that we consider commercially reasonable, we do not have insurance coverage for losses relating to an interruption of our research, development or manufacturing efforts caused by contamination, and the coverage or coverage limits of our insurance policies may not be adequate. In the event our losses exceed our insurance coverage, our financial condition would be adversely affected.

If a natural or man-made disaster strikes our research, development or manufacturing facilities, it could delay our progress developing and commercializing our drugs.

We manufacture our research and clinical supplies in a separate manufacturing facility located in Carlsbad, California. The facilities and the equipment we use to research, develop and manufacture our drugs would be costly to replace and could require substantial lead time to repair or replace. Our facilities may be harmed by natural or man-made disasters, including, without limitation, earthquakes, floods, fires and acts of terrorism, and in the event they are affected by a disaster, our development and commercialization efforts would be delayed. Although we possess insurance for damage to our property and the disruption of our business from casualties, this insurance may not be sufficient to cover all of our potential losses and may not continue to be available to us on acceptable terms, or at all.

Provisions in our certificate of incorporation, other agreements and Delaware law may prevent stockholders from receiving a premium for their shares.

Our certificate of incorporation provides for classified terms for the members of our board of directors. Our certificate also includes a provision that requires at least 66 percent of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15 percent or more of our voting stock, except in cases where certain directors approve the transaction or certain minimum price criteria and other procedural requirements are met.

Our certificate of incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. In addition, only our board of directors, chairman of the board or chief

executive officer can call special meetings of our stockholders. We also have implemented a stockholders' rights plan, also called a poison pill, which could make it uneconomical for a third party to acquire our company on a hostile basis. These provisions, as well as Delaware law and other of our agreements, may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over then current market prices, and may limit the ability of our stockholders to approve transactions that they think may be in their best interests. In addition, our board of directors has the authority to fix the rights and preferences of, and issue shares of preferred stock, which may have the effect of delaying or preventing a change in control of our company without action by our stockholders.

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The provisions of our convertible subordinated notes could make it more difficult or more expensive for a third party to acquire us. Upon the occurrence of certain transactions constituting a fundamental change, holders of the notes will have the right, at their option, to require us to repurchase all of their notes or a portion of their notes, which may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over the then current market prices.

In addition, our collaboration agreement with Genzyme regarding mipomersen provides that if we are acquired, Genzyme may elect to purchase all of our rights to receive payments under the mipomersen collaboration agreement for a purchase price to be mutually agree to by us and Genzyme, or, if we cannot agree, a fair market value price determined by an independent investment banking firm. This provision may make it more difficult or complicated for us to enter into an acquisition agreement with a potential acquirer.

Future sales of our common stock in the public market could adversely affect the trading price of our securities.

Future sales of substantial amounts of our common stock in the public market, or the perception that such sales could occur, could adversely affect trading prices of our securities. For example, we registered for resale 4.25 million shares of our common stock issuable upon the exercise of the warrant we originally issued to Symphony GenIsis Holdings. In addition, we have registered for resale our $2^{5}/_{8}$ percent convertible subordinated notes, including the approximately 11.1 million shares issuable upon conversion of the notes. The addition of any of these shares into the public market may have an adverse effect on the price of our securities.

Our business is subject to changing regulations for corporate governance and public disclosure that has increased both our costs and the risk of noncompliance.

Each year we are required to evaluate our internal controls systems in order to allow management to report on and our Independent Registered Public Accounting Firm to attest to, our internal controls as required by Section 404 of the Sarbanes-Oxley Act. As a result, we will incur additional expenses and will suffer a diversion of management's time. In addition, if we cannot continue to comply with the requirements of Section 404 in a timely manner, we might be subject to sanctions or investigation by regulatory authorities, such as the SEC, the Public Company Accounting Oversight Board, or PCAOB, or The Nasdaq Global Select Market. Any such action could adversely affect our financial results and the market price of our common stock.

Negative conditions in the global credit markets and financial services and other industries may adversely affect our business.

The global credit markets, the financial services industry, the U.S. capital markets, and the U.S. economy as a whole have been experiencing a period of substantial turmoil and uncertainty characterized by unprecedented intervention by the U.S. federal government and the failure, bankruptcy, or sale of various financial and other institutions. The impact of these events on our business and the severity of the economic crisis is uncertain. It is possible that the crisis in the global credit markets, the U.S. capital markets, the financial services industry and the U.S. economy may adversely affect our business, vendors and prospects as well as our liquidity and financial condition. More specifically, our insurance carriers and insurance policies covering all aspects of our business may become financially unstable or may not be sufficient to cover any or all of our losses and may not continue to be available to us on acceptable terms, or at all.

ITEM 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

We are exposed to changes in interest rates primarily from our long-term debt arrangements and, secondarily, investments in certain short-term investments. We invest our excess cash in highly liquid short-term investments that are typically held for the duration of the term of the respective instrument. We do not utilize derivative financial instruments, derivative commodity instruments or other market risk sensitive instruments, positions or transactions to manage exposure to interest rate changes. Accordingly, we believe that, while the securities we hold are subject to changes in the financial standing of the issuer of such securities, we are not subject to any material risks arising from changes in interest rates, foreign currency exchange rates, commodity prices, equity prices or other market changes that affect market risk sensitive instruments.

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ITEM 4. CONTROLS AND PROCEDURES

As of the end of the period covered by this Quarterly Report on Form 10-Q, we carried out an evaluation, under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended. Based on this evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of March 31, 2010. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to March 31, 2010.

An evaluation was also performed under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of any change in our internal control over financial reporting that occurred during our last fiscal quarter and that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting. That evaluation did not identify any change in our internal

control over financial reporting that occurred during our latest fiscal quarter and that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

We maintain disclosure controls and procedures that are designed to ensure that information required to be disclosed in our Exchange Act reports is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, as appropriate, to allow timely decisions regarding required disclosure. In designing and evaluating the disclosure controls and procedures, management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable and not absolute assurance of achieving the desired control objectives.

PART II — OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

On February 11, 2008, we notified Bruker Daltonics, Ibis' manufacturing and commercialization partner for the T5000 System, that we were initiating the formal dispute resolution process under Ibis' agreement with them. We asserted that Bruker's performance of its manufacturing, commercialization and product service obligations are unsatisfactory and fail to meet their obligations under this agreement. Executive level negotiations and formal mediation efforts failed to achieve resolution of this dispute. On May 22, 2008, Bruker filed a complaint against Isis Pharmaceuticals, Inc. and Ibis Biosciences, Inc. in Superior Court of Middlesex County, Massachusetts alleging monetary damages due to breach of contract by us and Ibis. We and Ibis filed an Answer, Affirmative Defenses and Counterclaim on July 14, 2008, alleging breach of contract by Bruker. Discovery remains in its early stage. As such, we have no basis on which to predict or record a loss related to this claim as of March 31, 2010. We will continue to represent and defend Ibis Biosciences in this matter.

ITEM 2. UNREGISTERED SALES OF EQUITY SECURITIES AND USE OF PROCEEDS

Not applicable

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable

ITEM 4. (REMOVED AND RESERVED)

Not applicable

ITEM 5. OTHER INFORMATION

On March 30, 2010 we entered a new lease agreement with an affiliate of BioMed Realty, L.P. Under the lease, BioMed will construct a new 176,000 square foot research facility in Carlsbad, California. Upon completion of construction, we will lease the new facility for a 20-year term and consolidate the majority of our operations in the new facility. The lease has an initial term of 20 years with an option to extend the lease for up to four five-year periods.

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Our rent under the new lease is based on a percentage of the total construction costs spent by BioMed to acquire the land and build the new facility. We will begin paying rent on January 1, 2012. Once the new facility is complete, we will be responsible for the costs associated with owning and maintaining the facility. Since our rent is based on a percentage of total construction costs spent by BioMed to acquire the land and build the new facility, and the facility is not yet built, it is difficult for us to calculate our future payment obligations under the lease. However, as of March 31, 2010, we estimate that the maximum potential future payments we may be required to make over the 20 year term of the lease are $172 million.

Under the lease we have an option to purchase the facility at the end of the fifth, sixth, seventh, eighth, ninth, fifteenth and twentieth year of the lease. The purchase price for the purchase options ending on the fifth through ninth year will be set based on the total construction costs spent by BioMed to acquire the land and build the new facility less rent payments made through the purchase date. The purchase price for the purchase options ending on the fifteenth and twentieth year will be based on fair market value at those times.

If we breach our obligations under the lease and do not cure the breach within specific time periods, BioMed may terminate the lease and we may be required to vacate the facility, pay the estimated present value of the future rent payments under the lease, or exercise our purchase option under the lease.

If BioMed cannot obtain the permits necessary for BioMed to construct the facility under the lease by specific dates, other than as a result of BioMed's gross negligence or willful misconduct, then BioMed may terminate the lease and will not be required to construct the facility, and we will not have obligations under the lease.

We also lease from BioMed an approximately 28,700 square foot facility that houses our manufacturing suites for our drug development business. On March 30, 2010 we amended the lease to extend the term through December 31, 2031, subject to four five-year options to extend the lease, and to obtain an option to purchase the manufacturing facility on similar terms as the purchase options described above.

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document

10.1	Amendment #1 to the Product Development and Commercialization Agreement between Regulus Therapeutics Inc. and Glaxo Group Limited dated February 24, 2010 (with certain confidential information deleted).
10.2	Exclusive License and Nonexclusive Option Agreement between Regulus Therapeutics Inc. and Glaxo Group Limited dated February 24, 2010 (with certain confidential information deleted).
10.3	Lease Agreement between the Registrant and BMR-Gazelle Court LLC dated March 30, 2010 (with certain confidential information deleted).
10.4	Second Amendment to Lease Agreement between the Registrant and BMR-2282 Faraday Avenue LLC dated March 30, 2010 (with certain confidential information deleted).
10.5	Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated March 30, 2010 (with certain confidential information deleted).
31.1	Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification by Chief Financial Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.

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Isis Pharmaceuticals, Inc.

(Registrant)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the Registrant and in the capacities and on the dates indicated.

Signatures	Title	Date
/s/ Stanley T. Crooke Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	May 6, 2010
/s/ B. Lynne Parshall B. Lynne Parshall, J.D.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	May 6, 2010

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R §§ 200.80(b)4, AND 240.24b-2 EXECUTION COPY

AMENDMENT #1 TO THE PRODUCT DEVELOPMENT AND COMMERCIALIZATION AGREEMENT

This **AMENDMENT #1 TO THE PRODUCT DEVELOPMENT AND COMMERCIALIZATION AGREEMENT** (this "**Amendment**") is entered into and made effective as of the 24th day of February 2010 (the "**Amendment Date**") by and between Regulus Therapeutics Inc., a Delaware corporation having its principal place of business at 1896 Rutherford Road, Carlsbad, CA 92008 ("**Regulus**"), and Glaxo Group Limited, a company existing under the laws of England and Wales, having its registered office at Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex, UB6 0NN, England ("**GSK**"). Regulus and GSK are each referred to herein by name or as a "**Party**" or, collectively, as "**Parties**."

RECITALS

WHEREAS, Regulus and GSK are parties to the Product Development and Commercialization Agreement dated April 17, 2008 (the "**Agreement**") and the Exclusive License and NonExclusive Option Agreement dated February 24, 2010 (the "**SPC-3649 Agreement**";

WHEREAS, GSK desires to include mir-122 as one of the four Collaboration Targets (and thereby including Regulus' drug discovery and development program focused on mir-122) under the Agreement, and Regulus desires to grant GSK such inclusion;

WHEREAS, the Parties desire to waive Section 12.4 of the Agreement in its entirely in connection with such inclusion of mir-122 as one of the four Collaboration Targets; and

WHEREAS, on or about the Amendment Date, Regulus shall deliver to GSK a convertible promissory note pursuant to which GSK shall lend Regulus the amount specified therein (the **"Second Convertible Promissory Note**").

NOW, THEREFORE, in consideration of the premises and mutual covenants herein contained, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties, intending to be hereby bound, do hereby agree as follows:

1.1 Interpretation.

1.1.1 The capitalized terms used and not otherwise defined in this Amendment shall have the meanings set forth in the Agreement.

1.1.2 *Other Defined Terms.*

(a) "**Lead Compound**" means the Collaboration Compound in the Regulus Mir-122 Program that is most advanced with respect to the Research Plan and Early Development Plan for the Regulus Mir-122 Program.

(b) "**Mir-122**" means the miRNA having the miRBase Accession Number [***], and the sequence [***].

(c) **"Regulus(') Mir-122 Program"** shall mean any miRNA Compound designed to interfere with or inhibit (i.e. "directed to" or "directed against") Mir-122, which compound was either (i) identified or discovered by Regulus or any of its Affiliates or any of its Founding Companies prior to the Amendment Date or (ii) is discovered or identified by or on behalf of Regulus or any of its Affiliates in accordance with the applicable Research Program).

(d) **"[***]"** means (a) the proprietary [***] compound [***] on the Amendment Date [***], and (b) any and all salts, crystalline and amorphous forms, and solvates (including hydrates) thereof. The sequence and chemistry of SPC-3649 is described in PCT Publication [***], published [***]. Solely with respect to Section 1.4 of this Amendment, the definition of [***] may be expanded as set forth in Section 1.4.2 of this Amendment.

(e) **"Stanford"** means The Board of Trustees of the Leland Stanford Junior University.

(f) **"Stanford License Agreement"** means the Co-Exclusive License Agreement dated August 31, 2005 among Stanford and the Parent Companies (as assigned by Isis to Regulus on July 13, 2009).

(g) **"Stanford Patent(s)"** means any Patent Right licensed under the Stanford License Agreement. A list of the Stanford Patents as of the Amendment Date is attached hereto under Exhibit I.

1.1.3 *Amendment and Restatement of Section 1.59 of Agreement.* Section 1.59 (definition of Field) of the Agreement, is hereby amended, restated and replaced in its entirety by the following:

"**1.59 "Field"** shall mean (a) the treatment and/or prophylaxis of any or all Indications and (b) also, to the extent that Regulus or GSK, whichever is the licensing Party hereunder, Controls diagnostic rights, the diagnosis of any or all Indications, to the extent such diagnostic rights are necessary

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or important to Commercialize a Licensed Product or where the absence of Control by the Commercializing Party, of diagnostic rights could reasonably be considered to materially adversely affect the sales of the Licensed Product; provided, however, that solely with respect to [***], "Field" shall be limited to the treatment and/or prophylaxis of hepatitis C virus."

1.1.4 All references to "Dollars" mean U.S. Dollars. The use of the singular form of a defined term also includes the plural form and *vice versa*, except where expressly noted. The use of the word "including" shall mean "including without limitation". The use of the words "herein," "hereof" or "hereunder," and words of similar import, refer to this Amendment in its entirety and not to any particular provision hereof.

1.2 Addition of Mir-122 as Collaboration Target and Program.

1.2.1 The Parties hereby agree that, effective as of the Amendment Date, Mir-122 shall be added as one of the four Collaboration Targets and that Regulus' Mir-122 Program will be added as a Program under the Agreement. The Parties agree that for purposes of adding the Regulus Mir-122 Program to the Agreement, the provisions of Section 3.2.1 will be deemed to be satisfied. Regulus will conduct the Regulus Mir-122 Program in accordance with the terms and conditions of the Agreement, including the provisions of Article 3 of the Agreement. Regulus will prepare and present a Research Plan for the Regulus Mir-122 Program to the Mir-122 Joint Program Subcommittee for approval within sixty (60) days of the Amendment Date. The Research Collaboration Term for the Regulus Mir-122 Program will commence as of the Amendment Date. GSK shall have a Program Option with respect to Regulus' Mir-122 Program, in accordance with the terms and conditions of the Agreement; *provided*, *however*, the restrictions set forth in Section 4.1.3 and Article 7 of the Agreement will not restrict or prevent Regulus or its Parent Companies from practicing outside the Field with respect to [***].

1.2.2 Within thirty (30) days of the Amendment Date, the parties will form a Joint Program Subcommittee under Section 2.2.1 of the Agreement that is specifically related to Regulus' Mir-122 Program (the **"Mir-122 Joint Program Subcommittee"**). For purposes of clarity, with respect to the Regulus Mir-122 Program, any reference in the Agreement to the Joint Program Subcommittee will be a reference to the Mir-122 Joint Program Subcommittee.

1.3 Waiver. For so long as GSK has not breached its payment obligation under Section 5.1, 5.3 and 5.4 of the SPC-3649 Agreement (and such breach has not been cured by the ninetieth (90^{th}) day following Regulus' written notice to GSK of such breach), Regulus hereby waives all of its right under Section 12.4 of the Agreement.

1.4 Future Rights.

1.4.1 If, at any point, after the Amendment Date, Regulus, or any of its Affiliates or Parent Companies engages [***] in discussions of an arrangement likely to result in the creation of Third Party License Pass-Through Costs related to the acquisition of the right to Develop or Commercialize [***], Regulus will notify GSK of such discussions, and Regulus will keep GSK reasonably informed as to the status and contents of such discussions and will consider in good faith any GSK comments with regard to the amount or structure of any Third Party License Pass-Through Costs payable for [***]; *provided*, *however*, this obligation will not apply to confidential discussions related to the acquisition of all or substantially all of [***] business. Also, if, at any point, after the Amendment Date Regulus, or any of its Affiliates or Parent Companies Controls the right to Develop and/or Commercialize [***] in the Field, then Regulus will promptly (but in any case within thirty (30) days) provide written notice to GSK and GSK will then have forty-five (45) days to conduct a due diligence evaluation of [***] and notify Regulus in writing whether GSK elects that [***] be added as a part of the Regulus Mir-122 Program as a Collaboration Compound. Along with such notice Regulus will send to GSK all information and data related to [***], including details of any Third Party License Pass-Through Costs payable for [***] reasonably necessary for GSK to conduct an evaluation of [***]. If GSK fails to notify Regulus within such forty- five (45) day period that GSK would like to add [***] to the Regulus Mir-122 Program, Regulus (or the applicable Parent Company) will be free to Develop and/or Commercialize [***] without any obligation to GSK. If GSK elects to add [***] to the Regulus Mir-122 Program, GSK shall obtain the rights thereto as set forth in Section 1.2 herein; provided, GSK agrees to pay [***] the costs (including but not limited to any upfront payments and equity premiums) to acquire control of [***] and [***] any Third Party License Pass-Through Costs applicable to [***], as Program-Specific Technology in accordance with Section 6.8.2 of the Agreement. Once [***] becomes a Collaboration Compound, GSK will pay to Regulus all previously unpaid milestones set forth in Section 6.4 of the Agreement, and as amended by Section 1.6 hereto for Milestone Events that have been achieved by [***] prior to the time it became a Collaboration Compound. By way of example only, if Regulus acquires Control of [***] after Phase 2

Clinical Trials have been initiated with [***] and GSK has not yet paid Regulus any milestones for the Regulus Mir-122 Program, GSK would pay Regulus the amounts corresponding to the Candidate Selection, Initiation of Phase 1 Clinical Trials and Initiation of Phase 2 Clinical Trials Milestone Events. For clarity purposes, such milestone(s) shall not be paid more than once with respect to Collaboration Compounds in the Regulus Mir-122 Program. If, prior to GSK's exercise of its Program Option for the Regulus Mir-122 Program, Regulus' Mir-122 Program is terminated such that it is no longer a Program under the Agreement, then GSK's right to add [***] to the Regulus Mir-122 Program under this Section 1.4 shall automatically terminate.

1.4.2 If in the same transaction (or series of transactions) that Regulus, its Affiliate or Parent Companies (as the case may be) obtained Control of [***], such Person also acquired Control of another miRNA Compound designed to interfere with or inhibit (i.e. "directed to" or "directed against") Mir-122 (each a **"Backup Mir-122 Compound"**) in the Field, then solely with respect to this Section 1.4, the definition of [***] will include such Backup Mir-122 Compound(s).

1.5 Purchase of Regulus Promissory Note. GSK agrees to lend Regulus an additional Five Million U.S. Dollars ($5,000,000). The loan shall be evidenced by a convertible promissory note, in the form of the Second Convertible Promissory Note, attached hereto as Exhibit A. Within [***] Business Days of the date on or after the Amendment Date that GSK receives an invoice from Regulus therefor, (a) GSK shall pay Regulus Five Million U.S. Dollars ($5,000,000) by wire transfer of immediately available funds to an account designated by Regulus in writing and (b) Regulus shall simultaneously deliver to GSK the executed Second Convertible Promissory Note in the amount of Five Million U.S. Dollars ($5,000,000).

1.6 Amendment to Milestone Payments. Notwithstanding Section 6.4 of the Agreement, there shall be no Discovery Milestone payment with respect to the Regulus Mir-122 Program, and instead the payment due upon the Regulus Mir-122 Program reaching Candidate Selection Stage shall be [***], payable within [***] days of receipt by GSK of an invoice sent from Regulus on or after the date of achievement of such Milestone Event.

1.7 Press Release; Disclosure of Amendment. On or promptly after the Amendment Date, the Parties shall individually or jointly issue a public announcement of the execution of this Amendment in form and substance substantially as set forth on Exhibit B.

1.8 Representations and Warranties of Regulus. Regulus hereby represents and warrants to GSK, as of the Amendment Date, that:

1.8.1 Regulus is the owner of, or otherwise has the right to grant all rights and licenses it purports to grant to GSK with respect to Regulus' Mir-122 Program under this Amendment;

1.8.2 Regulus has not withheld from GSK any material data or any material correspondence, including to or from any Regulatory Authority in Regulus' possession that would be material and relevant to a reasonable assessment of the scientific, commercial, safety, regulatory and commercial liabilities and commercial value of Regulus' Mir-122 Program; and

1.8.3 To the best of its knowledge and belief, without having conducted any special inquiry, no written claims have been made against Regulus or its Founding Companies alleging that any of the Regulus Patents are invalid or unenforceable or infringe any intellectual property rights of a Third Party.

1.9 Severability. If any provision hereof should be held invalid, illegal or unenforceable in any jurisdiction, the Parties shall negotiate in good faith a valid, legal and enforceable substitute provision that most nearly reflects the original intent of the Parties and all other provisions hereof shall remain in full force and effect in such jurisdiction and shall be liberally construed in order to carry out the intentions of the Parties hereto as nearly as may be possible. Such invalidity, illegality or unenforceability shall not affect the validity, legality or enforceability of such provision in any other jurisdiction.

1.10 Headings. Headings used herein are for convenience only and shall not in any way affect the construction of or be taken into consideration in interpreting this Amendment.

1.11 Further Actions. Each Party shall execute, acknowledge and deliver such further instruments, and do all such other acts, as may be necessary or appropriate in order to carry out the expressly stated purposes and the clear intent of this Amendment.

1.12 Counterparts. This Amendment may be signed in counterparts, each and every one of which shall be deemed an original, notwithstanding variations in format or file designation which may result from the electronic transmission, storage and printing of copies of this Amendment from separate computers or printers. Facsimile signatures and signatures transmitted via PDF shall be treated as original signatures.

1.13 Effect of the Agreement. Unless otherwise explicitly amended or changed hereby, all other terms and conditions of the Agreement shall remain in full force and effect.

1.14 Stanford License Considerations. For purposes of clarification, with respect to any sublicense granted by Regulus to GSK under the Stanford Patents, GSK acknowledges and agrees that (a) such sublicense is subject and subordinate to the terms and conditions of the Stanford License Agreement, (b) Stanford is a third party beneficiary to this Agreement as it relates to Articles 8, 9 and 10 of the Stanford License Agreement, such that Stanford may directly enforce Articles 8, 9 and 10 of the Stanford License Agreement against GSK, and (c) if Stanford terminates the Stanford License Agreement as it relates to Regulus (but not as it relates to the Agreement or this Amendment, GSK will assume (and be directly liable to Stanford for) all Third Party License Pass-Through Costs and all Third Party and Parent-Originated Rights and Obligations due Stanford in connection with the Agreement and this Amendment; provided, that if, by operation of this Section 1.14 GSK actually pays any such costs or fees to Stanford in satisfaction of any amounts owed under Section 4.5, Article 7 or Section 13.2 of the Stanford License Agreement, then GSK shall have the right, in addition to all other rights available at law and in equity, to [***] such payments against any other amounts GSK may owe to Regulus under the Agreement or this Amendment. If GSK exercises its right of [***] under this Section 1.14, then GSK will provide written notice to Regulus of such [***] claim.

1.15. Updates to Certain Schedules and Exhibits.

1.15.1 Schedule 6.8.2 of the Agreement is amended to include the Patent Rights listed in Exhibit C-1 attached to this Amendment.

1.15.2 Exhibit B of the Agreement is amended to include the Patent Rights listed in Exhibit C -2 attached to this Amendment.

1.15.3 Exhibit C of the Agreement is amended to include the Patent Rights listed in Exhibit C -3 attached to this Amendment.

1.15.4 Exhibit D of the Agreement is amended to include the Patent Rights listed in Exhibit C -4 attached to this Amendment.

1.15.5 Exhibit F of the Agreement is amended to include the In-License Agreement listed in Exhibit C - -5 attached to this Amendment.

1.16 Candidate Selection Criteria; Target Product Profile, PoC Criteria. The parties agree that (i) the Candidate Selection Criteria for Regulus' Mir-122 Program are set forth on Exhibit J attached to this Amendment; (ii) the initial draft Target Product Profile for Regulus' Mir-122 Program is set forth on Exhibit K attached to this Amendment; and (iii) the initial draft PoC Criteria for Regulus' Mir-122 Program are set forth on Exhibit L attached to this Amendment.

* - * - * - *

IN WITNESS WHEREOF, the Parties have caused this Amendment to be executed by their duly authorized representatives as of the Amendment Date.

Regulus Therapeutics Inc.

By: */s/ Kleanthis G. Xanthopoulos*
Name: Kleanthis G. Xanthopoulos
Title: President and CEO
Date:

Glaxo Group Limited

By: */s/ Victoria Whyte*
Name: Victoria Whyte
Title: For and on behalf of the Wellcome Foundation Limited
Date:

EXHIBIT A

Second Convertible Promissory Note

See attached.

THIS NOTE AND ANY SHARES ACQUIRED UPON CONVERSION OF THIS NOTE HAVE NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933, AS AMENDED, AND MAY NOT BE OFFERED, SOLD OR OTHERWISE TRANSFERRED, PLEDGED OR HYPOTHECATED EXCEPT PURSUANT TO AN EFFECTIVE REGISTRATION STATEMENT FILED UNDER SUCH ACT OR PURSUANT TO AN OPINION OF COUNSEL SATISFACTORY TO REGULUS THERAPEUTICS, ALNYLAM OR ISIS, AS APPLICABLE, THAT SUCH REGISTRATION IS NOT REQUIRED.

CONVERTIBLE PROMISSORY NOTE

$5,000,000 February24, 2010

No. 2

FOR VALUE RECEIVED, Regulus Therapeutics Inc., a Delaware corporation (the "Maker"), promises to pay to Glaxo Group Limited or its assigns (the "Holder") the principal sum of $5,000,000, together with interest on the unpaid principal balance of this Note from time to time outstanding at the rate per annum equal to [***] (as defined below) until paid in full. Subject to the conversion provisions set forth herein, all principal and accrued interest shall be due and payable on the earlier to occur of [***] (the "Anniversary Date") or (ii) a Change in Control (as defined below).

Interest on this Note shall be computed on the basis of a year of 365 days for the actual number of days elapsed and shall accrue, [***] on the last day of each [***] and as of the Anniversary Date (or any payment date prior thereto). All payments by the Maker under this Note shall be in immediately available funds.

1. Definitions. For purposes of this Note:

(a) "Change in Control" shall mean (i) any merger or consolidation to which the Maker is a party (except any merger or consolidation in which the holders of voting securities of the Maker immediately prior to such merger or consolidation continue to hold, immediately following such merger or consolidation and in approximately the same relative proportions as they held voting securities of the Maker, at least 51% of the voting power of the securities of (A) the surviving or resulting corporation, or (B) the parent corporation of the surviving or resulting corporation if the surviving or resulting corporation is a wholly-owned subsidiary of such parent corporation immediately following such merger or consolidation), (ii) the reduction below 50% in the aggregate beneficial ownership by the Guarantors (as defined below) of the outstanding voting power of the Maker or (iii) the sale of all or substantially all of the assets of the Maker. Notwithstanding the foregoing, a Qualified Financing will not be considered a Change in Control.

(b) "Guarantors" shall mean Alnylam Pharmaceuticals, Inc., a Delaware corporation ("Alnylam") and Isis Pharmaceuticals, Inc., a Delaware corporation ("Isis").

(c) "License and Option Agreement" shall mean the Product Development and Commercialization Agreement by and between the Maker and Holder dated April 17, 2008, as amended.

(d) "Prime Rate" shall mean for any [***] the prime rate of interest as of the first day of each such [***] as published from time to time by The Wall Street Journal, National Edition.

(e) "Qualified Financing" shall mean the first issuance of [***] by the Maker to bona fide institutional investors, with immediately available gross proceeds to the Maker of at least [***] (excluding any amount of this Note or other indebtedness of the Maker that convert into equity as part of such financing).

2. Automatic Conversion Upon Qualified Financing. Effective upon the closing of a Qualified Financing, all of the outstanding principal and accrued interest under this Note (the "Outstanding Amount") will automatically be converted into shares of the same class and series of capital stock of the Maker issued to other investors on the same basis as the investment by such investors in the Qualified Financing (the "Qualified Financing Securities") and at a conversion price equal to the price per share of Qualified Financing Securities paid by the other investors in the Qualified Financing (the "Qualified Financing Price"), with any resulting fraction of a share rounded down to the nearest whole share. Notwithstanding the foregoing, if the conversion of this Note pursuant to this Section 2(a) would otherwise result in the Holder, together with its affiliates, owning more than [***] of the outstanding capital stock of the Maker, calculated on an as-converted fully-diluted basis (including as outstanding shares of capital stock issuable upon exercise or conversion of all outstanding stock options, warrants or other convertible securities of the Maker, including any other convertible securities held by GSK), immediately following the conversion of the Note [***], the Outstanding Amount shall be converted either pursuant to the first sentence of this Section 2(a) or, [***], into (i) that number of shares of Qualified Financing Securities that would result in the Maker reaching, but not exceeding, [***], and (ii) an amount in cash equal to the difference between (A) the product of (1) the number of [***] Shares issued upon conversion, multiplied by (2) the Qualified Financing Price and (B) the Outstanding Amount. The Maker shall notify the Holder in writing of the anticipated occurrence of a Qualified Financing at least [***] days prior to the closing date of the Qualified Financing.

3. Repayment.

(a) If no Qualified Financing or Change of Control has occurred prior to the Anniversary Date, the Outstanding Amount, if any, will be [***] or, at the election of Regulus and with the consent of Alnylam and/or Isis, as the case may be, registered and unrestricted shares of Alnylam common stock and/or Isis common stock, with a value equal to [***] of the then Outstanding Amount, provided that shares of Alnylam and/or Isis common stock, as the case may be, are then traded on a national securities exchange and provided further that the average daily trading volume for such shares, as the case may be, is greater than [***] of the shares proposed to be issued to the Holder. For purposes of this Section 3(a), the value of one share of common stock shall be equal to the average closing price per share of such common stock, as reported on the national securities exchange on which the stock is then traded, during the [***] trading day period ending on (and including) the day that is two days prior to the Anniversary Date.

(b) In the event the Holder terminates the License and Option Agreement without cause or the Maker terminates the License and Option Agreement as a result of a material breach by the Holder, this Note may be prepaid in cash, in whole but not in part and without any pre-payment penalty, prior to the Anniversary Date at the election of the Maker and without the prior written consent of the Holder.

4. Events of Default. This Note shall become immediately due and payable without notice or demand (but subject to the conversion rights set forth herein) upon the occurrence at any time of any of the following events of default (individually, an "Event of Default" and collectively, "Events of Default"):

(a) the Maker fails to pay any of the principal or interest under this Note within 10 days of Maker's receipt of written notice that such amount is due and payable;

(b) the Maker or either Guarantor files any petition or action for relief under any bankruptcy, reorganization, insolvency or moratorium law or any other law for the relief of, or relating to, debtors, now or hereafter in effect, or seeks the appointment of a custodian, receiver, trustee (or other similar official) of the Maker or either Guarantor or all or any substantial portion of the Maker's or either Guarantor's assets, or makes any assignment for the benefit of creditors or takes any action in furtherance of any of the foregoing, or fails to generally pay its debts as they become due;

(c) an involuntary petition is filed, or any proceeding or case is commenced, against the Maker or either Guarantor (unless such proceeding or case is dismissed or discharged within 60 days of the filing or commencement thereof) under any bankruptcy, reorganization, arrangement, insolvency, adjustment of debt, liquidation or moratorium statute now or hereafter in effect, or a custodian, receiver, trustee, assignee for the benefit of creditors (or other similar official) is applied or appointed for the Maker or either Guarantor or to take possession, custody or control of any property of the Maker or either Guarantor, or an order for relief is entered against the Maker or either Guarantor in any of the foregoing; or

(d) termination of the License and Option Agreement by the Holder (or its assignee or successor under the License and Option Agreement) by reason of breach of the License and Option Agreement by the Maker.

Upon the occurrence of an Event of Default, the Holder shall have then, or at any time thereafter, all of the rights and remedies afforded creditors generally by the applicable federal laws or the laws of the Commonwealth of Massachusetts.

5. Guaranty.

(a) Guaranty of Payment. The Guarantors hereby jointly and severally guaranty to the Holder the due and full payment within [***] of delivery of the Guaranteed Default Notice (as defined below) and the performance of all of the indebtedness of the Maker to

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the Holder for principal and accrued interest under this Note (the "Obligations"). Subject to the conditions set forth herein, this Guaranty is an absolute, unconditional, joint and several and continuing guaranty of the full and punctual payment and performance of all of the Obligations and not of their collectibility only. Payments by the Guarantors hereunder may be required by the Holder on any number of occasions. All payments by the Guarantors hereunder shall be made to the Holder, in the manner and at the place of payment specified therefor in this Note. Notwithstanding the foregoing, the right of the Holder to demand and receive payment of any Obligation under this Section 5 shall be subject to the following conditions precedent: (i) the requested amount has become due and payable under this Note, (ii) the Holder has given written notice of the amount due to the Maker and the Guarantors, (iii) notwithstanding the notice delivered by the Holder under clause (ii), the Maker has not paid the Holder or its assigns such amount in full within 15 days of Maker's receipt of such notice (a "Guaranteed Default"), and (iv) the Guarantors have received written notice from the Holder of such Guaranteed Default (the "Guaranteed Default Notice").

(b) Waivers by Guarantors; Holder's Freedom to Act. Each Guarantor agrees that the Obligations will be paid and performed strictly in accordance with their respective terms, regardless of any law, regulation or order now or hereafter in effect in any jurisdiction affecting any of such terms or the rights of the Holder with respect thereto. Each Guarantor waives promptness, diligences, presentment, demand, protest, notice of acceptance, notice of any Obligations incurred and all other notices of any kind (except the Guaranteed Default Notice and any other notice specifically required to be given to such Guarantor under this Guaranty), all defenses which may be available by virtue of any valuation, stay, moratorium law or other similar law now or hereafter in effect, any right to require the marshalling of assets of the Maker or any other entity or other person primarily or secondarily liable with respect to any of the Obligations, any defense, setoff, counterclaim, or claim of any nature or kind arising from the present or future lack of validity or enforceability of any Obligation, and all suretyship defenses generally. Without limiting the generality of the foregoing, each Guarantor agrees to the provisions of any instrument evidencing or otherwise executed in connection with any Obligation and agrees that the obligations of such Guarantor hereunder shall not be released or discharged, in whole or in part, or otherwise affected by (a) the failure of the Holder to assert any claim or demand or to enforce any right or remedy against the Maker or any other entity or other person primarily or secondarily liable with respect to any of the Obligations; (b) any extensions, compromise, refinancing, consolidation or renewals of any Obligation; (c) any change in the time, place or manner of payment of any of the Obligations or any rescissions, waivers, compromise, refinancing, consolidation or other amendments or modifications of any of the terms or provisions of the Note or any other agreement evidencing, securing or otherwise executed in connection with any of the Obligations, (d) the addition, substitution or release of any entity or other person primarily or secondarily liable for any Obligation; (e) the adequacy of any means of obtaining repayment of any of the Obligations; or (f) any other act or omission which might in any manner or to any extent vary the risk of such Guarantor or otherwise operate as a release or discharge of such Guarantor, all of which may be done without notice to such Guarantor. To the fullest extent permitted by law, each Guarantor hereby expressly waives any and all rights or defenses arising by reason of (i) any "one action" or "anti-deficiency" law which would otherwise prevent the Holder from bringing any action, including any claim for a deficiency, or exercising any other right or remedy (including any right of set-off), against such Guarantor or (ii) any other law which in any other way would otherwise require any election of remedies by the Holder.

(c) Unenforceability of Obligations Against the Maker. If for any reason the Maker has no legal existence or is under no legal obligation to discharge any of the Obligations, or if any of the Obligations have become irrecoverable from the Maker by reason of the Maker's insolvency, bankruptcy or reorganization or by other operation of law or for any other reason, this Guaranty shall nevertheless be binding on each of the Guarantors to the same extent as if such Guarantor at all times had been the principal obligor on all such Obligations. In the event that acceleration of the time for payment of any of the Obligations is stayed upon the insolvency, bankruptcy or reorganization of the Maker, or for any other reason, all such amounts otherwise subject to acceleration under the terms of the Notes or any other agreement evidencing, securing or otherwise executed in connection with any Obligation shall be immediately due and payable by the Guarantors.

(d) Waiver of Rights Against Maker and Subrogation. Until the final payment and performance in full of all of the Obligations, each of the Guarantors shall not exercise and hereby forbears from exercising any rights against the Maker or any other person or entity (other than the other Guarantor) arising as a result of payment by such Guarantor hereunder, by way of subrogation, reimbursement, restitution, contribution or otherwise, and will not prove any claim in competition with the Holder in respect of any payment hereunder in any bankruptcy, insolvency or reorganization case or proceedings of any nature; the Guarantors will not claim any setoff, recoupment or counterclaim against the Maker in respect of any liability of the Guarantors to the Maker.

6. Miscellaneous.

(a) All payments by the Maker under this Note shall be made without set-off or counterclaim and be free and clear and without any deduction or withholding for any taxes or fees of any nature whatever, unless the obligation to make such deduction or withholding is imposed by law.

(b) No delay or omission on the part of the Holder in exercising any right under this Note shall operate as a waiver of such right or of any other right of the Holder, nor shall any delay, omission or waiver on any one occasion be deemed a bar to or waiver of the same or any other right on any future occasion.

(c) The Maker and every endorser or guarantor of this Note, regardless of the time, order or place of signing, hereby waives presentment, demand, protest and notices of every kind and assents to any permitted extension of the time of payment and to the addition or release of any other party primarily or secondarily liable hereunder.

(d) Any notices, requests and other communications hereunder shall be in writing and shall be personally delivered or sent by express delivery service, registered or certified air mail, return receipt requested, postage prepaid, or by facsimile (confirmed by prepaid registered or certified air mail letter or by international express delivery mail) (e.g., FedEx), and shall be deemed to have been properly served to the addressee upon receipt of such written communication, to the following addresses of the parties, or such other address as may be specified in writing to the other parties hereto:

if to Holder:
Glaxo Group Limited
980 Great West Road
Brentford, Middlesex TW8 9GS
United Kingdom
Facsimile: 44-20 8049 6904
Attention: Company Secretary

with a copy to:
GlaxoSmithKline
200 N 16th Street
Mail Code FP2355
Philadelphia, PA 19002
Facsimile: 215-751-5349
Attention: Vice President Legal Operations
Corporate Functions - US

if to Maker:
Regulus Therapeutics Inc.
1896 Rutherford Road
Carlsbad, California 92008

Facsimile:
Attention: President

if to Guarantors: Alnylam Pharmaceuticals, Inc.
300 Third Street, 3rd Floor
Cambridge, MA 02142
Facsimile: 617-551-8109
Attention: Vice President, Legal

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, California 92008
Facsimile: 760-268-4922
Attention: General Counsel

(e) The Holder agrees that no director or officer of the Maker or Guarantors shall have any personal liability for the repayment of this Note.

(f) This Note may not be amended or modified except by an instrument executed by the Maker, the Holder and each of the Guarantors.

(g) Until the conversion of this Note, the Holder shall not have or exercise any rights by virtue hereof as a member or stockholder of the Maker.

(h) All rights and obligations hereunder shall be governed by the laws of the Commonwealth of Massachusetts (without giving effect to principles of conflicts or choices of law) and this Note is executed as an instrument under seal.

MAKER:

REGULUS THERAPEUTICS INC

By: _____
Title: _____

GUARANTORS:

ALNYLAM PHARMACEUTICALS, INC.

By: _____
Title: _____

ISIS PHARMACEUTICALS, INC.

By: _____
Title: _____

EXHIBIT B

(Press Release)

Regulus Therapeutics and GlaxoSmithKline Establish New Collaboration to Develop and Commercialize microRNA Therapeutics Targeting miR-122

- miR-122 Represents a Novel "Host Factor" Strategy for Treatment of Hepatitis C Infection —

- Further Demonstration of Regulus Leadership in microRNA Science, Technology and Intellectual Property -

Carlsbad, CA., February XX, 2010 — Regulus Therapeutics Inc. today announced the establishment of a new collaboration with GlaxoSmithKline (GSK) to develop and commercialize microRNA therapeutics targeting microRNA-122 in all fields with Hepatitis C Viral infection (HCV) as the lead indication. Under the terms of the new collaboration, Regulus will receive additional upfront and early-stage milestone payments with the potential to earn more than $150 million in miR-122-related combined payments, and tiered royalties up to double digits on worldwide sales of products.

"This new collaboration with GSK demonstrates the clear scientific leadership that Regulus has established in advancing a whole new frontier of pharmaceutical research. microRNA therapeutics target the pathways of human diseases, not just single disease targets, and hold considerable promise as novel therapies across a broad range of unmet medical needs," said Kleanthis G. Xanthopoulos, Ph.D., President and Chief Executive Officer of Regulus. "It also further validates Regulus' microRNA product platform built on fundamental biology of human diseases and intellectual property, and also extends the therapeutic scope of our existing collaboration formed with GSK in 2008. Furthermore, the funding from this alliance supports Regulus' efforts in advancing high impact, novel medicines based on microRNA biology to patients."

The collaboration provides GSK with access to Regulus' comprehensive and robust intellectual property estate. Regulus exclusively controls patent rights covering miR-122 antagonists and their use as HCV therapeutics in the United States, Europe, and Japan, including but not limited to the patent families which encompass: the 'Sarnow' patent pertaining to the method of use of anti-miR-122 to inhibit HCV replication, the 'Esau' patent application claiming the use of anti-miRs targeting miR-122 as inhibitory agents, the 'Tuschl III' patent claiming composition of matter for miR-122 and complementary oligonucleotides, and the 'Manoharan' patent claiming antagomirs, including antagomirs targeting miR-122.

miR-122 is a liver-expressed microRNA that has been shown to be a critical endogenous "host factor" for the replication of HCV, and anti-miRs targeting miR-122 have been shown to block HCV infection (Jopling *et al.* (2005) *Science* 309, 1577-81). In earlier work, scientists at Alnylam and Isis demonstrated the ability to antagonize miR-122 *in vivo* using chemically modified single-stranded anti-miR oligonucleotides. Further, work

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by Regulus scientists and collaborators showed that inhibiting miR-122 results in significant inhibition of HCV replication in human liver cells, suggesting that antagonism of miR-122 may comprise a novel "host factor" therapeutic strategy. Regulus scientists have shown in multiple preclinical studies a robust HCV antiviral effect following inhibition of miR-122. Regulus plans to identify a clinical development candidate in the second half of 2010 and file an investigational new drug (IND) application in 2011.

About microRNAs

The discovery of microRNA in humans is one of the most exciting scientific breakthroughs in the last decade. microRNAs are small RNA molecules, typically 20 to 25 nucleotides in length, that do not encode proteins but instead regulate gene expression. Nearly 700 microRNAs have been identified in the human genome, and more than one-third of all human genes are believed to be regulated by microRNAs. As a single microRNA can regulate entire networks of genes, these new molecules are considered the master regulators of the genome. microRNAs have been shown to play an integral role in numerous biological processes including the immune response, cell-cycle control, metabolism, viral replication, stem cell differentiation and human development. Many microRNAs are conserved across multiple species indicating the evolutionary importance of these molecules as modulators of critical biological pathways. Indeed, microRNA expression or function has been shown to be significantly altered in many disease states, including cancer, heart failure and viral infections. Targeting microRNAs opens the possibility of a novel class of therapeutics and a unique approach to treating disease by modulating entire biological pathways.

About Hepatitis C Virus (HCV)

HCV infection is a disease with an estimated prevalence of 170 million patients worldwide, with more than 3 million patients in the United States. HCV shows significant genetic variation in worldwide populations due to its frequent rates of mutation and rapid evolution. There are six genotypes of HCV, with several subtypes within each genotype, which vary in prevalence across the different regions of the world. The response to treatment varies from individual to individual underscoring the inadequacy of existing therapies and highlights the need for combination therapies that not only target the virus but endogenous "host factors" as well. Strategies that include the Regulus miR-122 antagonist as part of emerging combination therapies to shorten duration of treatment and interferon use, improve the safety profile and sustained virologic response (SVR), increase the barrier to drug resistance, and address difficult-to-treat genotypes hold significant potential to expand the limited therapies available to physicians treating HCV patients.

About Regulus Therapeutics Inc.

Regulus Therapeutics is a biopharmaceutical company leading the discovery and development of innovative new medicines based on microRNAs. Regulus is targeting microRNAs as a new class of therapeutics by working with a broad network of academic collaborators and leveraging oligonucleotide drug discovery and development expertise from its founding companies Alnylam Pharmaceuticals (*Nasdaq:ALNY*) and Isis Pharmaceuticals (*Nasdaq:ISIS*). Regulus is advancing microRNA therapeutics towards

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the clinic in several areas including hepatitis C infection, cardiovascular disease, fibrosis, oncology, immuno-inflammatory diseases, and metabolic diseases. Regulus' intellectual property estate contains both the fundamental and core patents in the field as well as over 600 patents and more than 300 pending patent applications pertaining primarily to chemical modifications of oligonucleotides targeting microRNAs for therapeutic applications. In 2008, Regulus entered into a major alliance with GlaxoSmithKline to discover and develop microRNA therapeutics for immuno-inflammatory diseases. For more information, visit www.regulusrx.com.

Forward-Looking Statements

This press release includes forward-looking statements regarding the future therapeutic and commercial potential of Regulus', Alnylam's, and Isis' business plans, technologies and intellectual property related to microRNA therapeutics being discovered and developed by Regulus, including statements regarding expectations around the relationship between GSK and Regulus. Any statement describing Regulus', Alnylam's, and Isis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are described as such parties' goals. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such products. Such parties' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause their results to differ materially from those expressed or implied by such forward-looking statements. Although these forward-looking statements reflect the good faith judgment of the management of each such party, these statements are based only on facts and factors currently known by Regulus', Alnylam's, and Isis' management as the case may be. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Regulus', Alnylam's, and Isis' programs are described in additional detail in Alnylam's and Isis' annual reports on Form 10-K for the year ended December 31, 2008, and their most recent quarterly reports on Form 10-Q which are on file with the SEC. Copies of these and other documents are available from Alnylam or Isis.

Additions to Schedule 6.8.2 of the Agreement

[***]

EXHIBIT C-2

Additions to Exhibit B of the Agreement

Patents and Applications Licensed to Regulus by Isis on the Effective Date

[***]

EXHIBIT C-3

Additions to Exhibit C of the Agreement

[***]

EXHIBIT C-4

Additions to Exhibit D of the Agreement

Listing of Patent Rights Licensed to Regulus

[***]

EXHIBIT C-5

Additions to Exhibit F of the Agreement

[***]

EXHIBIT I

[***]

EXHIBIT J

Candidate Selection Criteria for Regulus' Mir-122 Program

[***]

EXHIBIT K

Draft Target Product Profile for Regulus' Mir-122 Program

[***]

EXHIBIT L

Draft PoC Criteria for Regulus' Mir-122 Program

[***]

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R §§ 200.80(b)4, AND 240.24b-2

EXCLUSIVE LICENSE AND NONEXCLUSIVE OPTION AGREEMENT

BETWEEN

GLAXO GROUP LIMITED

AND

REGULUS THERAPEUTICS INC.

This **EXCLUSIVE LICENSE AND NONEXCLUSIVE OPTION AGREEMENT** (this "**Agreement**") is entered into and made effective as of the 24th day of February 2010 (the "**Effective Date**") by and between Regulus Therapeutics Inc., a Delaware corporation having its principal place of business at 1896 Rutherford Road, Carlsbad, CA 92008 ("**Regulus**"), and Glaxo Group Limited, a company existing under the laws of England and Wales, having its registered office at Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex, UB6 0NN, England ("**GSK**"). Regulus and GSK are each referred to herein by name or as a "**Party**" or, collectively, as "**Parties**."

RECITALS

WHEREAS, Regulus is a Delaware corporation that is jointly owned by Isis Pharmaceuticals, Inc. ("**Isis**") and Alnylam Pharmaceuticals, Inc. ("**Alnylam**" and together with Isis, Regulus' "**Founding Companies**", and each a "**Founding Company**");

WHEREAS, Regulus and GSK are parties to the Product Development and Commercialization Agreement dated April 17, 2008, as amended (the "**Existing Collaboration**");

WHEREAS, Regulus possesses proprietary technology and know-how related to the research, discovery, identification, synthesis and development of single-stranded oligonucleotide miRNA Antagonists in the Field (each as defined below);

WHEREAS, GSK possesses expertise in the pharmaceutical research, development, manufacturing and commercialization of human pharmaceuticals, and GSK is interested in developing miRNA Antagonists as drug products in the Field;

WHEREAS, GSK may obtain from Santaris a license to commercialize the miRNA Compound known as SPC-3649;

WHEREAS, GSK desires, upon obtaining certain rights to SPC-3649 from Santaris, to obtain from Regulus an exclusive license to develop and commercialize SPC-3649 in the Field; and Regulus desires to grant GSK such rights, all on the terms and conditions set forth herein; and

WHEREAS, GSK may, during the term of this Agreement, desire to obtain from Regulus a nonexclusive license to certain other patents in the Field, and in such case, GSK and Regulus agree to negotiate in good faith, in accordance with the terms and conditions of this Agreement to the extent possible, and in accordance with the Agreement between Regulus and Garching Innovation GmbH, as appropriate.

NOW, THEREFORE, in consideration of the premises and mutual covenants herein contained, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties, intending to be hereby bound, do hereby agree as follows:

ARTICLE 1
DEFINITIONS

1.1 The capitalized terms used and not otherwise defined in this Agreement shall have the meanings set forth in Exhibit A attached hereto unless context dictates otherwise. All references to "Dollars" mean U.S. Dollars. The use of the singular form of a defined term also includes the plural form and *vice versa*, except where expressly noted. The use of the word "including" shall mean "including without limitation". The use of the words "herein," "hereof" or "hereunder," and words of similar import, refer to this Agreement in its entirety and not to any particular provision hereof.

ARTICLE 2
[***] OPTION

2.1 Option to License the [***] Patents. If GSK provides Regulus with written notice of a desire to negotiate in good faith to obtain a nonexclusive license to the [***] Patents, then Regulus and GSK shall, in good faith, use commercially reasonable efforts to conclude a written license agreement (the ***"[***] Sublicense"***) within sixty (60) days of such written notice for the grant by Regulus to GSK of a worldwide, nonexclusive, royalty-bearing, sublicenseable (in accordance with Section 3.1.2 below) license, under the [***] Patents solely to Develop, Manufacture and Commercialize SPC-3649 in the Field; provided, that, such license will (a) be subject to the terms and conditions of those certain agreements between Regulus and those certain Third Parties in effect as of the Effective Date and as listed on Exhibit G, and (b) have a maximum royalty rate to be paid by GSK under such agreement capped at the Third Party License Pass-Through Costs under the [***]. Upon GSK's and Regulus' execution of the [***]Sublicense, and subject to the terms

and conditions of the [***] Sublicense, (i) the [***] shall be deemed listed on Exhibit G, and (ii) the [***] Patents shall be deemed included in the definition of Regulus Patents and therefore subject to ARTICLE 3.

ARTICLE 3
GRANT OF LICENSE RIGHTS

3.1 License Grants to GSK.

3.1.1 *Development and Commercialization License*. Subject to the terms and conditions of this Agreement (including but not limited to the limitations set forth in this ARTICLE 3) and those certain agreements between Regulus and those certain Third Parties in effect as of the Effective Date and as listed on Exhibit G, Regulus hereby grants to GSK a worldwide, exclusive, royalty-bearing, sublicenseable (in accordance with Section 3.1.2 below) license, under the Regulus Patents solely to Develop, Manufacture and Commercialize SPC-3649 in the Field.

3.1.2 *Sublicense Rights*. Subject to the terms and conditions of this Agreement (including but not limited to the limitations set forth in this ARTICLE 3) and those certain agreements between Regulus and those certain Third Parties in effect as of the Effective Date and as listed on Exhibit G, GSK shall have the right to grant to its Affiliates and/or Third Parties sublicenses under the license granted under Section 3.1.1 above *solely* to continue the Development, Manufacture or Commercialization of SPC-3649; provided, that, (a) each such sublicense shall be subject and subordinate to, and consistent with, the applicable terms and conditions of this Agreement; (b) GSK may not grant a sublicense to Santaris or any of Santaris' Affiliates; and (c) GSK cannot sublicense the Stanford Patents. GSK shall provide Regulus with a copy of any sublicense granted pursuant to this Section 3.1.2 within thirty (30) days after the execution thereof. Such copy may be redacted to exclude confidential scientific information and other sensitive information required by a Sublicensee or GSK to be kept confidential; provided, that for agreements that are entered into by GSK or its Affiliates after the Effective Date that materially relate to the Regulus Patents, GSK will reasonably endeavor to facilitate the communication of information between the Parties with respect to any subsequent Development activities by GSK to the extent required by those certain agreements between Regulus and those certain Third Parties in effect as of the Effective Date and as listed on Exhibit G. Regulus may share such copy or information with its Founding Companies and relevant Third Party licensors who have a contractual right and material need to know such information under obligations of confidentiality which are no less strict than the confidentiality obligations imposed upon Regulus hereunder. GSK will remain responsible for the performance of its Affiliates and Sublicensees, and will ensure that all such Affiliates and Sublicensees comply with the relevant provisions of this Agreement.

3.1.3 *Retained Rights; No Implied Licenses*. The exclusive license granted to Regulus by Alnylam pursuant to Section 2.2(a) of the Regulus License Agreement is subject to Alnylam's retained right to use and exploit Alnylam's Founding Company Know-How and Founding Company Patents solely to support its own internal Research in the Alnylam Field (each as defined in the Regulus License Agreement). The exclusive license granted to Regulus by Isis pursuant to Section 2.2(a) of the Regulus License Agreement is subject to Isis' retained right to use and exploit Isis' Founding Company Know-How and Founding Company Patents solely to support its own internal Research in the Isis Field (each as defined in the Regulus License Agreement). All rights in and to Regulus Patents not expressly licensed to GSK

hereunder, under the Existing Collaboration or pursuant to the operation of the relevant applicable express provisions of this Agreement or the Existing Collaboration, and any other Patent Rights or Know-How of Regulus or its Founding Companies or Affiliates, are hereby retained by Regulus or such Founding Company or Affiliate. Except as expressly provided in this Agreement, no Party will be deemed by estoppel or implication to have granted the other Parties any license or other right with respect to any intellectual property of such Party.

3.1.4 *Stanford License Considerations.* For purposes of clarification, with respect to the sublicense granted by Regulus to GSK under the Stanford Patents, GSK acknowledges and agrees that (a) such sublicense is subject and subordinate to the terms and conditions of the Stanford License Agreement, (b) Stanford is a third party beneficiary to this Agreement as it relates to Articles 8, 9 and 10 of the Stanford License Agreement, such that Stanford may directly enforce Articles 8, 9 and 10 of the Stanford License Agreement against GSK, and (c) if Stanford terminates the Stanford License Agreement as it relates to Regulus (but not as it relates to this Agreement), GSK will assume (and be directly liable to Stanford for) all Third Party License Pass-Through Costs and all Third Party and Founding Company-Originated Rights and Obligations due Stanford in connection with this Agreement; provided, that if, by operation of this Section 3.1.4 GSK actually pays any such costs or fees to Stanford in satisfaction of any amounts owed under Section 4.5, Article 7 or Section 13.2 of the Stanford License Agreement, then GSK shall have the right, in addition to all other rights available at law and in equity, to [***]. If GSK exercises its right of [***] under this Section 3.1.4, then GSK will provide written notice to Regulus of such [***] claim.

3.2 Santaris Option to [***] Patents. Regulus hereby agrees that it will grant Santaris an exclusive license under the [***] Patents to develop and commercialize SPC-3649 within the Field (the "**Santaris License**") if (a) GSK obtains rights to Develop and/or Commercialize SPC-3649 from Santaris or its Affiliates ("**SPC-3649 Rights")**, and (b) if GSK subsequently ceases development of SPC-3649 and returns rights to SPC-3649 to Santaris (the **"Santaris Option Trigger Date"**); provided, (a) Santaris gives Regulus a written notice electing to obtain the Santaris License on or before 5:00 p.m. Pacific time on the sixtieth (60^{th}) day following the Santaris Option Trigger Date, and (b) Regulus and Santaris execute the Santaris License within sixty (60) days following Regulus' receipt of such election notice. The Santaris License, if granted, will include the material terms listed in Exhibit H attached hereto. Regulus and GSK agree that if GSK obtains the SPC-3649 Rights, then Santaris is an intended third party beneficiary of this Agreement with respect to the rights granted to Santaris pursuant to this Section 3.2 and that Santaris may exercise its rights under this Section 3.2 independently. For clarity, if Santaris does not give Regulus a written notice electing to obtain the Santaris License on or before 5:00 p.m. Pacific time on the 60^{th} day following the Santaris Option Trigger Date, or if Regulus and Santaris have not executed the Santaris License within sixty (60) days following Regulus' receipt of such election notice, then in each case this Section 3.2 will be null and void.

ARTICLE 4
[Intentionally Left Blank]

ARTICLE 5
SPC-3649 MILESTONES AND ROYALTIES; SPC-3649 PAYMENTS

5.1 Upfront Payment to Regulus. In partial consideration for the license and option granted to GSK under Section 2.1 and ARTICLE 3 of this Agreement, GSK shall pay to Regulus, by wire transfer of immediately available funds to an account designated by Regulus in writing, a one-time-only initial non-refundable, non-creditable fee of Three Million U.S. Dollars ($3,000,000) no later than ten (10) Business Days after receipt by GSK of an invoice sent from Regulus on or after the Effective Date of this Agreement (the "**Upfront Payment**").

5.2 [Intentionally Left Blank].

5.3 SPC-3649 Exclusive License Fees. If (a) GSK obtains the SPC-3649 Rights; and (b) [***] GSK obtaining such SPC-3649 Rights, then GSK shall pay to Regulus a non-refundable, non-creditable fee of [***] within thirty (30) days of receipt by GSK of an invoice sent from Regulus regarding such fee; provided, however, if [***] GSK obtaining such SPC-3649 Rights and GSK subsequently [***]], then GSK shall pay to Regulus a non-refundable, non-creditable fee [***] within thirty (30) days of receipt by GSK of an invoice sent from Regulus regarding such fee. Notwithstanding the foregoing, if GSK either: (i) holds the SPC-3649 Rights as of [***] and GSK has not previously paid Regulus the [***] fee under this Section 5.3 or (ii) GSK licenses the SPC-3649 Rights after [***], GSK shall pay to Regulus a non-refundable, non-creditable fee of [***] within thirty (30) days of receipt of an invoice from Regulus for such fee.

5.4 Milestone Payments for Achievement of Milestone Events. GSK shall pay to Regulus the applicable milestone payments as set forth in the table below in this Section 5.4 within thirty (30) days of receipt by GSK of an invoice sent from Regulus on or after the date of first achievement of such Milestone Event by SPC-3649 or an SPC-3649 Product. GSK shall send Regulus a written notice thereof promptly following the date of achievement of each Milestone Event.

Milestone Event (each a "Milestone Event")	**Milestone Payment* US$Million ("m")**
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]
TOTAL Potential Milestones	$ [***]

*Each milestone will be paid only once upon the first achievement of the Milestone Event.

†Such milestone will only be payable if, at the time such milestone is achieved there is a Valid Claim within the Regulus Patents, which covers the [***] of SPC-3649 or an SPC-3649 Product; provided, however, that if there is no Valid Claim at the time of such Milestone Event, then (a) GSK must pay to Regulus [***] percent ([***]%) of such milestone payment upon [***] of an SPC-3649 Product in any country in the [***]; and (b) if a Pending Claim within the Regulus Patents issues such that it is a Valid Claim in the [***] prior to the [***] anniversary of the date of the First Commercial Sale described in clause (a) above, then GSK will pay Regulus the remaining [***] percent ([***]%) of such milestone within thirty (30) days of receipt by GSK of an invoice sent from Regulus on or after the date of the issuance of the applicable Pending Claim.

5.5 Royalty Payments for SPC-3649 to Regulus.

5.5.1 *GSK Patent Royalty*. As partial consideration for the license granted to GSK hereunder, GSK will pay to Regulus royalties on Annual worldwide Net Sales of any SPC-3649 Product sold by GSK, its Affiliates or Sublicensees during a calendar year, on a country-by-country basis, in the Field in the countries of the Territory in which there is a Valid Claim in the Field within the Regulus Patents, which covers the [[***] SPC-3649 or such SPC-3649 Product, in the amounts as follow (the "**GSK Patent Royalty**"). For purposes of clarity, in no event shall GSK be obligated to pay royalties more than once with respect to the same unit of SPC-3649 Product and GSK shall owe no royalties or milestones to Regulus, its Affiliates, Founding Companies, or anyone on behalf of Regulus, its Affiliates, or Founding Companies, on SPC-3649 Product under any terms of the Existing Collaboration.

(a) GSK shall pay to Regulus the royalties at the percentages as described in the table below:

Annual Worldwide Net Sales (U.S. $ Million) of SPC-3649 Product per Calendar Year US$Million ("m")	**Applicable Royalty Rate**
up to $1000m	[***]%
$1000m up to $2000m	[***]%
$2000m up to $3000m	[***]%
> $3000m	[***]%

(b) In the event any Combination Product(s) are sold, royalties on such Combination Products will be determined pursuant to the definition of "**Net Sales**" on Exhibit A.

(c) The royalty rates in the table above are incremental rates, which apply only for the respective increment of Annual worldwide Net Sales described in the Annual worldwide Net Sales column. Thus, once a total Annual worldwide Net Sales figure is achieved for the year,

the royalties owed on any lower tier portion of Annual worldwide Net Sales are not adjusted up to the higher tier rate.

5.5.2 *Royalty Adjustment.* If there are no Valid Claims within the Regulus Patents that [***] an SPC-3649 Product sold in a particular country, the GSK Patent Royalty set forth in Section 5.5.1 shall be reduced to [***] percent ([***]%) of the GSK Patent Royalty rates above in such countries where a Pending Claim within the Regulus Patents claims [***] an SPC-3649 Product has not yet been issued. For the avoidance of doubt, for such Pending Claims, GSK shall pay Regulus [***] percent ([***]%) of the GSK Patent Royalty set forth in Section 5.5.1 above, and shall pay the remaining [***] percent ([***]%) of the GSK Patent Royalty into an escrow account, until such time as a Valid Claim within the Regulus Patents issues that covers [***] an SPC-3649 Product being sold in the country of sale, provided that such Valid Claim must issue within [***] years of date of First Commercial Sale of an SPC-3649 Product (the **"Royalty Tail Period"**). In the event such Valid Claim issues during the Royalty Tail Period, (i) the escrow account and any interest thereon shall be paid to Regulus and (ii) GSK will pay the full GSK Patent Royalty in such countries starting only from the date of such issuance of the Valid Claim and shall not owe any GSK Patent Royalty in such countries for any preceding period. In the event that no such Valid Claim issues during the Royalty Tail Period, then the escrowed amounts and any interest thereon shall be returned to GSK and any obligations GSK may have had with respect to the Pending Claims shall cease. If GSK maintains sole control over such escrow account then GSK shall be solely responsible for the costs and expenses associated with maintaining such escrow account, otherwise GSK and Regulus shall be

mutually responsible for the costs and expenses associated with maintaining such escrow account; provided, that the Parties must mutually agree (such agreement not to be unreasonably withheld) before taking any action that would cause GSK to lose sole control of such escrow account. If a Valid Claim within the Regulus Patents that [***] an SPC-3649 Product issues after the Royalty Tail Period, then GSK will pay Regulus the full GSK Patent Royalty in such countries starting only from the date of such issuance of the Valid Claim and shall not owe any GSK Patent Royalty in such countries for any preceding period.

5.5.3 *Patent Royalty Term*.

(a) For Pending Claims, GSK's obligation to pay the GSK reduced GSK Patent Royalty in Section 5.5.2 above with respect to SPC-3649 Product or Combination Product will continue on a country-by-country basis from the date of First Commercial Sale of an SPC-3649 Product or Combination Product in the Field until the end of the Royalty Tail Period.

(b) For Valid Claims, GSK's obligation to pay the GSK Patent Royalty Rate above with respect to SPC-3649 Product or Combination Product will continue on a country-by-country basis from the date of First Commercial Sale of an SPC-3649 Product or Combination Product in the Field until the date of expiration of the last Valid Claim in the Field within the Regulus Patents, which covers [***] of an SPC-3649 Product or Combination Product. In no circumstance will GSK pay a GSK Patent Royalty or any other royalty hereunder beyond the date of expiration of the last Valid Claim in the Field.

5.6 Pass Through Payments.

5.6.1 *Regulus Obligations.* Regulus will be solely responsible for paying [***] Total License Pass-Through Costs (a) [***] (as such term is defined in the Existing Collaboration) except pursuant to the terms of Section 5.6.2 herein, and (b) due under the [***].

5.6.2 *Obligations for Future IP.* After the Effective Date, Regulus may wish to in-license or acquire rights to Patent Rights controlled by a Third Party (such a Third Party in-license or acquisition agreement being an **"Additional Third Party Agreement"**) which, if so licensed or acquired, may be included in the Regulus Patents licensed to GSK under Section 3.1. Once Regulus has executed such Additional Third Party Agreement, Regulus will offer such Third Party Patent Rights to GSK (including a description of the payments paid or potentially payable by Regulus thereunder). At such time, if GSK wishes to include such Third Party Patents under the licenses granted under Section 3.1, GSK will notify Regulus of its desire to do so and the Parties will fairly and in good faith allocate upfront payments or ongoing payment obligations between SPC-3649 and compounds that are not SPC-3649. If GSK does not agree to

reimburse Regulus for the amount of any upfront or similar acquisition payments fairly allocated to SPC-3649, and to be responsible for the payment of GSK's share of any [***] payments under the Additional Third Party Agreement, then the Third Party Patents acquired or in-licensed by Regulus under the Additional Third Party Agreement will not be considered a Regulus Patent licensed to GSK under this Agreement. Should the Parties agree, then GSK shall reimburse Regulus for GSK's share of such amounts within forty-five (45) days after GSK's receipt of an invoice from Regulus therefor.

5.6.3 *Regulus Obtains Rights to SPC-3649.* Should Regulus obtain SPC-3649 Rights from Santaris or its Affiliate(s), then this Agreement shall automatically terminate, and the provisions of [***] the Product Development and Commercialization Agreement between the Parties of even date herewith shall apply.

5.7 Third Party Licenses. Subject to Section 5.6.2, GSK shall be solely responsible for obtaining any licenses from Third Parties that GSK determines, in its sole discretion, are required in order to lawfully develop, manufacture, and commercialize SPC-3649 in the Field for patents (i) not included within the license grants to GSK as set forth in Section 3.1 of this Agreement and/or (ii) not included within Regulus Patents.

5.8 Minimum Royalty Payment. Notwithstanding any other provision of this Agreement, at a minimum, GSK will pay Regulus a minimum royalty on Net Sales of SPC-3649 Product by GSK, its Affiliates or Sublicensees equal to (a) the Total Pass Through Costs that are royalty obligations Regulus must pay under [***]; and (b) any royalty payments GSK agrees to pay under Section 2.1 and/or Section 5.6.2.

5.9 Payments.

5.9.1 *Commencement.* Beginning with the Calendar Quarter in which the First Commercial Sale of an SPC-3649 Product is made and for each Calendar Quarter thereafter, royalty payments shall be made by GSK to Regulus under this Agreement within forty-five (45) days following the end of each such Calendar Quarter. Each royalty payment shall be accompanied by a report, summarizing Net Sales for each SPC-3649 Product during the

relevant Calendar Quarter and the calculation of royalties (including the details of any adjustments or credits permitted under this Agreement), if any, due thereon. Notwithstanding the foregoing, in the event that no royalties are payable in respect of a given Calendar Quarter, the Payor shall submit a royalty report so indicating.

5.9.2 *Mode of Payment*. All payments under this Agreement shall be payable, in full, in U.S. Dollars, regardless of the country(ies) in which sales are made. For the purposes of computing Net Sales of SPC-3649 Product sold in a currency other than U.S. Dollars, such

currency shall be converted into U.S. Dollars as calculated at the actual average rates of exchange for the pertinent quarter or year to date, as the case may be, as reasonably used by the Payor in producing its quarterly and annual accounts. Such payments shall be without deduction of exchange, collection or other charges.

5.9.3 *Records Retention*. Commencing with the First Commercial Sale of SPC-3649 Product, the Payor shall keep complete and accurate records pertaining to the sale of SPC-3649 Product, for a period of three (3) calendar years after the year in which such sales occurred, and in sufficient detail to permit the Payee to confirm the accuracy of the Net Sales or royalties paid by the Payor hereunder.

5.10 Audits. During the term of this Agreement and for a period of three (3) years thereafter, at the request and expense of the Payee, the Payor shall permit an independent, certified public accountant of nationally recognized standing appointed by the Payee, and reasonably acceptable to the Payor, at reasonable times and upon reasonable notice, but in no case more than once per calendar year thereafter, to examine such records as may be necessary for the sole purpose of verifying the calculation and reporting of Net Sales and the correctness of any royalty payment and Annual worldwide Net Sales payments made under this Agreement for any period within the preceding three (3) years. The independent, certified public accountant shall disclose to the Payee only the royalty amounts which the independent auditor believes to be due and payable hereunder to the Payee and shall disclose no other information revealed in such audit. GSK shall also have the right to have audited, in accordance with this Section 5.10, the relevant books and records of Regulus as may be necessary for the sole purpose of verifying the amount of Third Party License Pass-Through Costs or Total License Pass-Through Costs actually being paid by Regulus. Any and all records of the audited Party examined by such independent accountant shall be deemed such audited Party's Confidential Information which may not be disclosed by said independent, certified public accountant to any Third Party or (except for the information expressly sought to be confirmed by the auditing Party as set forth in this Section 5.5) to the auditing Party. If, as a result of any inspection of the books and records of the audited Party, it is shown that (x) the audited Party's payments under this Agreement were less than the royalty amount which should have been paid, then such audited Party shall make all payments required to be made, or (y) the amount paid to Third Parties by the audited Party as pass-through costs is less than the amount for which reimbursement was requested from the auditing Party to cover such pass-through costs, then the audited Party shall pay the auditing Party the difference between such amounts, to eliminate any discrepancy revealed by said inspection, within sixty (60) days and shall be entitled to a credit with respect to any overpayment made by such audited Party. The auditing Party shall pay for such audits, except

that in the event that the royalty payments and/or the amount of pass-through costs made by the audited Party were less than ninety percent (90%) of the undisputed amounts (or the amount requested to be reimbursed by the auditing Party, with respect to pass-through costs) that should have been paid during the period in question, the audited Party shall pay the reasonable costs of the audit.

5.11 Taxes.

5.11.1 *Sales or Other Transfers*. The recipient of any transfer under this Agreement of Regulus Patents, GSK Technology, and/or Confidential Information, as the case may be, shall be solely responsible for any sales, use, value added, excise or other taxes applicable to such transfer.

5.11.2 *Withholding Tax*. The Parties acknowledge and agree that, under applicable laws in effect as of the Effective Date, GSK shall not be required to withhold any taxes from the Withholding-Free Payments payable to Regulus under this Agreement. Consequently, GSK agrees not to withhold any taxes from payment of the Withholding-Free Payments hereunder. Any tax paid or required to be withheld by GSK for the benefit of Regulus on account of any royalties or other payments (other than the Withholding-Free Payments) payable to Regulus under this Agreement shall be deducted from the amount of royalties or other payments otherwise due. GSK shall secure and send to Regulus proof of any such taxes withheld and paid by GSK for the benefit of Regulus, and shall, at Regulus' request, provide reasonable assistance to Regulus in recovering such taxes. Regulus warrants that Regulus is a Delaware corporation as of the Effective Date and, prior to the payment of royalties by GSK hereunder, shall be a resident for tax purposes in the US and that, as of such time, Regulus shall be entitled to relief from United Kingdom income tax under the terms of the double tax agreement between the UK and the US. Regulus shall notify GSK immediately in writing in the event that Regulus ceases to be entitled to such relief. Pending receipt of formal certification from the UK Inland Revenue, GSK may pay royalty income and any other payments (other than the Withholding-Free Payments) under this Agreement to Regulus by deducting tax at the applicable rate specified in the double tax treaty between the UK and US. Regulus agrees to indemnify and hold harmless GSK against any loss, damage, expense or liability arising in any way from a breach of the above warranties or any future claim by a UK tax authority or other similar body alleging that GSK was not entitled to deduct withholding tax on such payments at source at the treaty rate, except that Regulus' indemnification obligation under this Section 5.11.2 shall not apply to GSK's payment of the Withholding-Free Payments. Regulus shall timely complete all US and UK tax forms as reasonably requested by GSK with respect to taxes withheld pursuant to this Section 5.11.2. Notwithstanding the foregoing, if UK tax law

changes after the Effective Date and GSK has a good faith belief that such change requires GSK to withhold taxes from any Withholding-Free Payment, then GSK will first notify Regulus in writing thereof, and GSK may withhold taxes from the Withholding-Free Payments that GSK reasonably believes is necessary to comply with the new UK tax law, consistently applied by GSK to similarly situated licensing arrangements.

ARTICLE 6
OWNERSHIP OF INTELLECTUAL PROPERTY AND PATENT PROSECUTION

6.1 Ownership. The determination of inventorship shall be made in accordance with United States patent laws.

6.2 Prosecution and Maintenance of Patents.

6.2.1 *Regulus Patents*. At Regulus' expense, Regulus shall (but shall not be obligated to) control and be responsible for all aspects of the Prosecution, Maintenance, enforcement and defense of all Regulus Patents.

6.2.2 *Duty to Notify of Competitive Infringement*. If either Party learns of an infringement, unauthorized use, misappropriation or threatened infringement by a Third Party with respect to any Regulus Patent in the Field, by reason of the Development, Manufacture, use or Commercialization in the Field of a product that contains or consists of a miRNA Compound as an active ingredient that is substantially identical in structure, sequence or composition to SPC-3649 ("**Competitive Infringement**"), such Party shall promptly notify the other Party and shall provide such other Party with available evidence of such Competitive Infringement.

6.3 [***]

ARTICLE 7
CONFIDENTIALITY

7.1 Confidentiality; Exceptions. Except to the extent expressly authorized by this Agreement or otherwise agreed in writing, the Parties agree that, during the Agreement Term and for five (5) years thereafter, the receiving Party (the "**Receiving Party**"), its Affiliates and, with respect to Regulus, its Founding Companies, shall keep confidential and shall not publish or otherwise disclose or use for any purpose other than as provided for in this Agreement any Know-How or other confidential and proprietary information and materials, patentable or otherwise, in any form (written, oral, photographic, electronic, magnetic, or otherwise) which is disclosed to it by the other Party (the "**Disclosing Party**"), its Affiliates or, with respect to Regulus, its Founding Companies or otherwise received or accessed by a Receiving Party in the course of performing its obligations or exercising its rights under this Agreement, including, but not limited to trade secrets, know-how, inventions or discoveries, proprietary information,

formulae, processes, techniques and information relating to the past, present and future marketing, financial, and research and development activities of any product or potential product or useful technology of the Disclosing Party, its Affiliates or Founding Companies and the pricing thereof (collectively, "**Confidential Information**"), except to the extent that it can be established by the Receiving Party that such Confidential Information:

7.1.1 was in the lawful knowledge and possession of the Receiving Party, its Affiliates or Founding Companies prior to the time it was disclosed to, or learned by, the Receiving Party, its Affiliates or Founding Companies, or was otherwise developed independently by the Receiving Party, its Affiliates or Founding Companies, as evidenced by written records kept in the ordinary course of business, or other documentary proof of actual use by the Receiving Party, its Affiliates or Founding Companies;

7.1.2 was generally available to the public or otherwise part of the public domain at the time of its disclosure to the Receiving Party, its Affiliates or Founding Companies;

7.1.3 became generally available to the public or otherwise part of the public domain after its disclosure and other than through any act or omission of the Receiving Party, its Affiliates or Founding Companies in breach of this Agreement; or

7.1.4 was disclosed to the Receiving Party, its Affiliates or Founding Companies, other than under an obligation of confidentiality, by a Third Party who had no obligation to the Disclosing Party, its Affiliates or Founding Companies not to disclose such information to others.

7.2 Authorized Disclosure. Except as expressly provided otherwise in this Agreement, a Receiving Party or its Affiliates may use and disclose, to Third Parties or the Founding Companies, Confidential Information of the Disclosing Party as follows: (i) with respect to any such disclosure of Confidential Information, under confidentiality provisions no less restrictive than those in this Agreement, and solely in connection with the performance of its obligations or exercise of rights granted or reserved in this Agreement (including, without limitation, the rights to Develop and Commercialize SPC-3649, and to grant licenses and sublicenses hereunder), provided, that Confidential Information may be disclosed by a Receiving Party to a governmental entity or agency without requiring such entity or agency to enter into a confidentiality agreement with such Receiving Party if such Receiving Party has used reasonable efforts to impose such requirement without success and disclosure to such governmental entity or agency is necessary for the performance of the Receiving Party's obligations hereunder; (ii) to the extent such disclosure is reasonably necessary in filing or prosecuting patent, copyright and trademark applications, complying with applicable governmental regulations, obtaining

Regulatory Approvals, conducting Pre-Clinical Studies or Clinical Studies, marketing SPC-3649, or as otherwise required by applicable law, regulation, rule or legal process (including the rules of the SEC and any stock exchange); provided, however, that if a Receiving Party or any of its Affiliates or Founding Companies is required by law or regulation (including the rules of the SEC and any stock exchange) to make any such disclosure of a Disclosing Party's Confidential Information it will, except where impracticable for necessary disclosures, for example, but without limitation, in the event of medical emergency, give reasonable advance notice to the Disclosing Party of such disclosure requirement and will use its reasonable efforts to secure confidential treatment of such Confidential Information required to be disclosed; (iii) in communication with actual or potential investors, merger partners, acquirers, consultants, or professional advisors on a need to know basis, in each case under confidentiality provisions no less restrictive than those of this Agreement; (iv) in communication with actual or potential licensees outside the Field on a need to know basis, in each case under confidentiality provisions no less restrictive than those of this Agreement and such Confidential Information may be redacted to exclude confidential scientific information, the name of the Disclosing Party and other sensitive information reasonably required by the Disclosing Party to be kept confidential; (v) to the extent and only to the extent that such disclosure is required to comply with existing expressly stated contractual obligations owed to such Party's, its Affiliate's or Founding Company's licensor with respect to any intellectual property licensed under this Agreement; or (vi) to the extent mutually agreed to in writing by the Parties. If a Founding Company receives GSK's Confidential Information as permitted pursuant to this Section 7.2, such Founding Company may only use and disclose GSK's

Confidential Information solely in accordance with this Section 7.2 under confidentiality provisions no less restrictive than those in this Agreement and solely as and to the extent required (x) by law, court order or an existing expressly stated contractual requirement of a licensor to Regulus Patents, or (y) for such Founding Company to perform its rights or obligations in connection with this Agreement.

7.3 Press Release; Disclosure of Agreement. On or promptly after the Effective Date, the Parties shall individually or jointly issue a public announcement of the execution of this Agreement in form and substance substantially as set forth on Exhibit D. Except to the extent required to comply with applicable law, regulation, rule or legal process or as otherwise permitted in accordance with this Section 7.3, neither Party nor such Party's Affiliates or Founding Companies shall make any public announcements, press releases or other public disclosures concerning this Agreement or the terms or the subject matter hereof or thereof, without the prior written consent of the other, which shall not be unreasonably withheld. Notwithstanding the foregoing, (a) GSK and its Affiliates may make disclosures pertaining

solely to SPC-3649, provided, however, that GSK will immediately notify (and provide as much advance notice as possible to) Regulus of any event materially related to SPC-3649 (including any Regulatory Approval) so that the Parties may analyze the need for or desirability of publicly disclosing or reporting such event; provided any press release or other similar public communication by GSK related to efficacy or safety data and/or results of SPC-3649 will be submitted to Regulus for review at least five (5) Business Days (to the extent permitted by law) in advance of such proposed public disclosure, Regulus shall have the right to expeditiously review and recommend changes to such communication and the Party whose communication has been reviewed shall in good faith consider any changes that are timely recommended by the reviewing Parties and (b) to the extent information regarding this Agreement has already been publicly disclosed, either Party (or its Affiliates or the Founding Companies) may subsequently disclose the same information to the public without the consent of the other Party. In addition, GSK understands that Regulus is a private company, and that Regulus may disclose the financial terms of this Agreement to potential, investors and investment bankers, in each case, under confidentiality provisions similar to and no less restrictive than those of this Agreement. Each Party shall give the other Party a reasonable opportunity (to the extent consistent with law) to review all material filings with the SEC describing the terms of this Agreement prior to submission of such filings, and shall give due consideration to any reasonable comments by the non-filing Party relating to such filing, including without limitation the provisions of this Agreement for which confidential treatment should be sought.

7.4 Remedies. Notwithstanding Section 11.1, each Party shall be entitled to seek, in addition to any other right or remedy it may have, at law or in equity, a temporary injunction, without the posting of any bond or other security, enjoining or restraining the other Party from any violation or threatened violation of this ARTICLE 7.

ARTICLE 8
REPRESENTATIONS AND WARRANTIES

8.1 Representations and Warranties of Both Parties. Each Party hereby represents and warrants to the other Party, as of the Effective Date, that:

8.1.1 such Party is duly organized, validly existing and in good standing under the laws of the jurisdiction of its incorporation or organization and has full corporate power and authority to enter into this Agreement and to carry out the provisions hereof;

8.1.2 such Party has taken all necessary action on its part to authorize the execution and delivery of this Agreement and the performance of its obligations hereunder;

8.1.3 this Agreement has been duly executed and delivered on behalf of such Party, and constitutes a legal, valid, binding obligation, enforceable against it in accordance with the terms hereof;

8.1.4 the execution, delivery and performance of this Agreement by such Party will not constitute a default under nor conflict with any agreement, instrument or understanding, oral or written, to which it is a party or by which it is bound, nor violate any law or regulation of any court, governmental body or administrative or other agency having jurisdiction over such Party; and

8.1.5 no government authorization, consent, approval, license, exemption of or filing or registration with any court or governmental department, commission, board, bureau, agency or instrumentality, domestic or foreign, under any applicable laws, rules or regulations currently in effect, is or will be necessary for, or in connection with, the transaction contemplated by this Agreement or any other agreement or instrument executed in connection herewith, or for the performance by it of its obligations under this Agreement and such other agreements except as may be required to obtain HSR clearance.

8.2 Representations and Warranties of Regulus. Regulus hereby represents and warrants to GSK, as of the Effective Date, that:

8.2.1 Regulus is the owner of, or otherwise has the right to grant all rights and licenses it purports to grant to GSK with respect to the Regulus Patents under this Agreement;

8.2.2 To the best of its knowledge and belief, without having conducted any special inquiry, Regulus is not aware of any other intellectual property rights owned or controlled by Regulus or any of its Founding Companies that are necessary for GSK to develop, manufacture, or commercialize SPC-3649 in the Field; and

8.2.3 To the best of its knowledge and belief, without having conducted any special inquiry, no written claims have been made against Regulus or its Founding Companies alleging that any of the Regulus Patents are invalid or unenforceable or infringe any intellectual property rights of a Third Party.

8.3 Regulus Covenants. Regulus hereby covenants to GSK, that:

8.3.1 [Intentionally Left Blank]; and

8.3.2 with respect to the rights to Regulus Patents existing as of the Effective Date, Regulus will not enter into any agreement after the Effective Date with a Founding Company or a Third Party that would restrict or limit (i) the licenses granted by Regulus to GSK under Section 3.1 above, or (ii) the options granted by Regulus to GSK under Section 2.1. For purposes of clarification, this Section 8.3.2 will not restrict Regulus' ability to Prosecute and Maintain the Regulus Patent Rights in accordance with Section 6.2.

8.4 GSK Covenants. GSK hereby covenants to Regulus that:

8.4.1 GSK shall notify Regulus in writing within ten (10) Business Days of the date that GSK or its Affiliate acquires from Santaris or one of Santaris' Affiliates the SPC-3649 Rights; and

8.4.2 If GSK or its Affiliate acquires from Santaris or one of Santaris' Affiliates a license to develop and/or commercialize SPC-3649, Regulus and GSK will jointly prepare a research plan for SPC-3649; provided, that (i) GSK shall not be required to share with Regulus or any Founding Company any confidential information if doing so would result in a breach of an agreement between GSK and Santaris; and (ii) GSK will have the sole decision making authority with respect to such research plan.

8.5 DISCLAIMER. EXCEPT AS OTHERWISE EXPRESSLY SET FORTH IN THIS AGREEMENT, NEITHER PARTY NOR ITS AFFILIATES OR PARENT COMPANIES MAKES ANY REPRESENTATION OR EXTENDS ANY WARRANTY OF ANY KIND, EITHER EXPRESS OR IMPLIED, INCLUDING, BUT NOT LIMITED TO, ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR ANY WARRANTY THAT ANY PATENT RIGHTS LICENSED TO THE OTHER PARTY HEREUNDER ARE VALID OR ENFORCEABLE OR THAT THEIR EXERCISE DOES NOT INFRINGE OR MISAPPROPRIATE ANY PATENT RIGHTS OR OTHER INTELLECTUAL PROPERTY RIGHTS OF THIRD PARTIES. GSK UNDERSTANDS THAT SPC-3649 IS THE SUBJECT OF ONGOING CLINICAL RESEARCH AND DEVELOPMENT AND THAT REGULUS CANNOT ASSURE THE SAFETY, USEFULNESS OR COMMERCIAL OR TECHNICAL VIABILITY OF SUCH COMPOUNDS.

ARTICLE 9
INDEMNIFICATION; INSURANCE

9.1 Indemnification by GSK. Subject to this ARTICLE 9, GSK shall indemnify, defend and hold harmless Regulus, and its Affiliates and Founding Companies, and its or their respective directors, officers, employees and agents, from and against any and all liabilities, damages, losses, costs and expenses including, but not limited to, the reasonable fees of attorneys and other professionals (collectively "**Losses**"), arising out of or resulting from any and all Third Party suits, claims, actions, proceedings or demands ("**Claims**") based upon:

9.1.1 the negligence, recklessness or wrongful intentional acts or omissions of GSK and/or its Affiliates and its or their respective directors, officers, employees and agents, in connection with GSK's performance of its obligations or exercise of its rights under this Agreement;

9.1.2 any breach of any representation or warranty or express covenant made by GSK under ARTICLE 8 or any other provision under this Agreement;

9.1.3 the Development or Manufacturing activities that are conducted by and/or on behalf of GSK or its Affiliates or Sublicensees, including handling and storage and manufacture by and/or on behalf of GSK or its Affiliates or Sublicensees of SPC-3649 or SPC-3649 Product for the purpose of conducting Development or Commercialization by or on behalf of GSK or its Affiliates or Sublicensees; or

9.1.4 the Commercialization by or on behalf of GSK, its Affiliates or Sublicensees of SPC-3649 or SPC-3649 Product;

except, in each case above, to the extent such Claim arose out of or resulted from or is attributable to the negligence, recklessness or wrongful intentional acts or omissions of Regulus and/or its Affiliate, Founding Company, licensee, Sublicensee or contractor, and its or their respective directors, officers, employees and agents, or breach of any representation or warranty or express covenant made by Regulus or any of its Founding Companies hereunder.

9.1.5 For the avoidance of doubt, (i) the term "**Loss**" or "**Losses**" of Section 9.1 does not include liabilities, damages, losses, costs, expenses, or fees of attorneys and other professionals arising out of or resulting from any suit brought by a Founding Company to enforce any patent or claim thereof owned by or controlled by said Founding Company; and (ii) the term "**Claim**" or "**Claims**" of Section 9.1 does not include suits, claims, actions, proceedings or demands brought by a Founding Company to enforce any patent or claim thereof owned by or controlled by said Founding Company.

9.2 Indemnification by Regulus. Regulus shall indemnify, defend and hold harmless GSK, and its Affiliates, and its or their respective directors, officers, employees and agents, from and against any and all Losses, arising out of or resulting from any and all Claims based upon any breach of any representation or warranty or express covenant made by Regulus under ARTICLE 8 or any other provision under this Agreement; except, to the extent such Claim arose out of or resulted from or is attributable to the negligence, recklessness or wrongful intentional acts or omissions of GSK and/or its Affiliate, licensee, Sublicensee or contractor and its or their respective directors, officers, employees and agents or breach of any representation or warranty or express covenant made by GSK hereunder.

9.3 Procedure. In the event that any Person entitled to indemnification under Section 9.1 or Section 9.2 (an "**Indemnitee**") is seeking such indemnification, such Indemnitee shall (i) inform, in writing, the indemnifying Party of a Claim as soon as reasonably practicable after such Indemnitee receives notice of such Claim, (ii) permit the indemnifying Party to assume direction and control of the defense of the Claim (including the sole right to settle

it at the sole discretion of the indemnifying Party, provided, that such settlement or compromise does not admit any fault or negligence on the part of the Indemnitee, nor impose any obligation on, or otherwise materially adversely affect, the Indemnitee or other Party), (iii) cooperate as reasonably requested (at the expense of the indemnifying Party) in the defense of the Claim, and (iv) undertake reasonable steps to mitigate any loss, damage or expense with respect to the Claim(s). Notwithstanding anything in this Agreement to the contrary, the indemnifying Party shall have no liability under Section 9.1 or 9.2, as the case may be, with respect to Claims settled or compromised by the Indemnitee without the indemnifying Party's prior written consent.

9.4 Insurance. GSK hereby represents and warrants to Regulus that it is self-insured against liability and other risks associated with its activities and obligations under this Agreement in such amounts and on such terms as are customary for prudent practices for large companies in the pharmaceutical industry for the activities to be conducted by GSK under this Agreement. GSK shall furnish to Regulus evidence of such self-insurance, upon request.

9.5 LIMITATION OF CONSEQUENTIAL DAMAGES. EXCEPT FOR CLAIMS OF A THIRD PARTY WHICH ARE SUBJECT TO INDEMNIFICATION UNDER THIS ARTICLE 9 OR AS OTHERWISE EXPRESSLY STATED IN THIS AGREEMENT, NEITHER REGULUS NOR GSK, NOR ANY OF THEIR AFFILIATES OR SUBLICENSEES NOR THE PARENT COMPANIES WILL BE LIABLE TO THE OTHER PARTY TO THIS AGREEMENT, ITS AFFILIATES OR ANY OF THEIR SUBLICENSEES NOR THE PARENT COMPANIES, FOR ANY INCIDENTAL, CONSEQUENTIAL, SPECIAL, PUNITIVE OR OTHER INDIRECT DAMAGES OR LOST OR IMPUTED PROFITS OR ROYALTIES, LOST DATA OR COST OF PROCUREMENT OF SUBSTITUTE GOODS OR SERVICES, WHETHER LIABILITY IS ASSERTED IN CONTRACT, TORT (INCLUDING NEGLIGENCE AND STRICT PRODUCT LIABILITY), INDEMNITY OR CONTRIBUTION, AND IRRESPECTIVE OF WHETHER THAT PARTY OR ANY REPRESENTATIVE OF THAT PARTY HAS BEEN ADVISED OF, OR OTHERWISE MIGHT HAVE ANTICIPATED THE POSSIBILITY OF, ANY SUCH LOSS OR DAMAGE.

ARTICLE 10
TERM AND TERMINATION

10.1 Agreement Term; Expiration. Unless earlier terminated pursuant to Section 5.6.3 or the other provisions of this ARTICLE 10, this Agreement shall be effective as of the Effective Date and shall continue in full force and effect until the date of the expiration of all payment obligations by GSK under this Agreement, (the "**Agreement Term**").

10.2 Termination for Cause.

10.2.1 Either Party (in such capacity, the "**Non-breaching Party**") may, without prejudice to any other remedies available to it at law or in equity, terminate this Agreement in the event the other Party (in such capacity, the "**Breaching Party**") shall have materially breached or defaulted in the performance of any of its material obligations hereunder, and such default shall have continued for ninety (90) days after written notice thereof was provided to the Breaching Party by the Non-breaching Party, such notice describing with particularity and in detail the alleged material breach.

10.2.2 *Disagreement.* Notwithstanding any of the foregoing, if the Parties reasonably and in good faith disagree as to whether there has been a material breach under Section 10.2.1 above, the Party which seeks to dispute that there has been a material breach may contest the allegation in accordance with Section 11.1. Notwithstanding the above sentence, the cure period for any allegation made in good faith as to a material breach under this Agreement will run from the date that written notice was first provided to the Breaching Party by the Non-breaching Party. Any termination of the Agreement under this Section 10.2 shall become effective at the end of such ninety (90) day period, unless the Breaching Party has cured any such breach or default prior to the expiration of such ninety (90) day period. The right of either Party to terminate this Agreement shall not be affected in any way by such Party's waiver or failure to take action with respect to any previous default.

10.3 GSK Unilateral Termination Rights. GSK shall have the right, at its sole discretion, exercisable at any time during the Agreement Term, to terminate (i) its license under ARTICLE 3 (including all other provisions of this Agreement related thereto), or (ii) this Agreement in its entirety, for any reason or for no reason at all, upon ninety (90) days written notice to Regulus. Except as set forth in Section 10.5, GSK shall not have any additional cost, liability, expense, or obligation of any kind whatsoever on account of any termination under this Section 10.3. For purposes of clarity, in no event shall GSK have the right to exercise its right to terminate the Agreement under this Section 10.3 following Regulus' notice of termination under Section 10.2.

10.4 Termination for Insolvency.

10.4.1 Either Party may terminate this Agreement, if, at any time, the other Party shall file in any court or agency pursuant to any statute or regulation of any state or country, a petition in bankruptcy or insolvency or for reorganization or for an arrangement or for the appointment of a receiver or trustee of the Party or of substantially all of its assets, or if the other Party proposes a written agreement of composition or extension of substantially all of its debts, or if the other Party shall be served with an involuntary petition against it, filed in any insolvency proceeding, and such petition shall not be dismissed within ninety (90) days after the filing thereof, or if the other Party shall propose or be a party to any dissolution or liquidation, or if the other Party shall make an assignment of substantially all of its assets for the benefit of creditors.

10.4.2 All rights and licenses granted under or pursuant to any Section of this Agreement are and shall otherwise be deemed to be for purposes of Section 365(n) of Title 11, United States Code (the "**Bankruptcy Code**") licenses of rights to "intellectual property" as defined in Section 101(56) of the Bankruptcy Code. The Parties shall retain and may fully exercise all of their respective rights and elections under the Bankruptcy Code. Upon the bankruptcy of any Party, the non-bankrupt Party shall further be entitled to a complete duplicate of, or complete access to, any such intellectual property, and such, if not already in its possession, shall be promptly delivered to the non-bankrupt Party, unless the bankrupt Party elects to continue, and continues, to perform all of its obligations under this Agreement.

10.5 Accrued Rights; Surviving Provisions of the Agreement; Certain Clarifications.

(a) Termination, relinquishment or expiration of this Agreement for any reason shall be without prejudice to any rights that shall have accrued to the benefit of any Party prior to such termination, relinquishment or expiration including, without limitation, the payment obligations under ARTICLE 5 hereof and any and all damages arising from any breach hereunder. Such termination, relinquishment or expiration shall not relieve any Party from obligations which are expressly indicated to survive termination of this Agreement.

(b) The provisions of Sections 3.1.4 (solely to the extent Articles 8, 9 or 10 of the Stanford Agreement survive and are applicable to GSK as a current or former sublicensee under the Stanford Agreement), 5.9.3, 5.10, 5.11, 8.5, 10.5 and ARTICLE 6, ARTICLE 7, ARTICLE 9, and ARTICLE 11 shall survive the termination or expiration of this Agreement for any reason, in accordance with their respective terms and conditions, and for the duration stated, and where no duration is stated, shall survive indefinitely.

ARTICLE 11
MISCELLANEOUS

11.1 Dispute Resolution by Binding Arbitration. Any controversy or claim arising out of or under this Agreement, or the breach thereof, shall be finally resolved by binding arbitration, held in New York City, New York, and administered by the American Arbitration Association under its Commercial Arbitration Rules. Judgment on the award rendered by the arbitrator(s) may be entered in any court having jurisdiction thereof. The Parties shall make reasonable efforts to appoint three (3) arbitrators, who are each mutually acceptable to GSK and Regulus, within forty-five (45) days of the initiation of the arbitration; in the event they are unsuccessful and do not agree to extend the time period, then the arbitrators shall be appointed in accordance with the rules. The Parties shall share the expenses for the arbitrators, but shall otherwise be responsible for their own fees in relation to such arbitration. Until such time as arbitrators are appointed, the Parties may seek judicial relief for interim measures, such as injunctive relief, in any court having competent jurisdiction. For clarity, the Parties understand and agree that binding arbitration pursuant to this Section 11.1 shall not apply to alter or modify the indemnity obligations of the respective Parties under ARTICLE 9, but arbitration may be sought to interpret such obligations. For clarity, the Arbitrators shall not have authority or discretion to decide any matter other than the matter for decision before them, and any such decision shall not include any award or determination which would amend the applicable terms of the Agreement.

11.2 Governing Law. This Agreement and any dispute arising from the performance or breach hereof shall be governed by and construed and enforced in accordance with the laws of the State of Delaware, U.S.A., without reference to conflicts of laws principles.

11.3 Assignment. This Agreement shall not be assignable by either Party to any Third Party or Founding Company, in the case of Regulus, (except as expressly stated below) without the prior written consent of the other Party hereto, such consent not to be unreasonably withheld. Notwithstanding the foregoing, (a) either Party may assign this Agreement, without any consent of the other Party, to an Affiliate, to a Third Party, or to the Founding Company of such Party, in the case of Regulus, that acquires all or substantially all of the business or assets of such Party to which the subject matter of this Agreement pertains (whether by merger, reorganization, acquisition, sale or otherwise), and (b) Regulus may assign or transfer its rights to receive royalties and milestones under this Agreement (but no liabilities), without GSK's consent, to an Affiliate, to its Founding Company, or to a Third Party in connection with a payment factoring transaction. Notwithstanding the foregoing, each Party shall have the right to assign this Agreement, in whole or in part, to its Affiliate or Founding Company, in the case of Regulus,

without the prior written consent of the other Party; provided, that, such assignee is able to exercise diligent efforts equivalent to those required to be exercised by such assigning Party and otherwise perform all of the obligations of the assigning Party hereunder and assumes in writing all of the relevant liabilities and obligations of the assigning Party hereunder. No assignment and transfer shall be valid and effective unless and until the assignee/transferee shall agree in writing to be bound by the provisions of this Agreement. Notwithstanding anything in this Section 11.3 to the contrary, any Person to whom Regulus assigns this Agreement or any of its rights under this Agreement shall be required to complete any paperwork requested by GSK pursuant to Section 5.11.2; such obligations shall continue to any other Person(s) thereafter, if any, to whom this Agreement and any rights hereunder are assigned. The terms and conditions of this Agreement shall be binding upon and shall inure to the benefit of the successors, heirs, administrators and permitted assigns of the Parties. Any assignment not in accordance with the foregoing shall be void.

11.4 Performance Warranty. Each Party hereby acknowledges and agrees that it shall be responsible for the full and timely performance as and when due under, and observance of all the covenants, terms, conditions and agreements set forth in, this Agreement by its Affiliate(s) and Sublicensees.

11.5 Force Majeure. No Party shall be held liable or responsible to the other Party nor be deemed to be in default under, or in breach of any provision of, this Agreement for failure or delay in fulfilling or performing any obligation of this Agreement when such failure or delay is due to *force majeure*, and without the fault or negligence of the Party so failing or delaying. For purposes of this Agreement, *force majeure* is defined as causes beyond the reasonable control of a Party, which may include, without limitation, acts of God; acts, regulations, or laws of any government; war; civil commotion; destruction of production facilities or materials by fire, flood, earthquake, explosion or storm; labor disturbances; epidemic and failure of public utilities or common carriers. In such event the Party so failing or delaying shall immediately notify the other Party of such inability and of the period for which such inability is expected to continue. The Party giving such notice shall thereupon be excused from such of its obligations under this Agreement as it is thereby disabled from performing for so long as it is so disabled for up to a maximum of ninety (90) days, after which time the Parties will negotiate in good faith any modifications of the terms of this Agreement that may be necessary to arrive at an equitable solution, unless the Party giving such notice has set out a reasonable timeframe and plan to resolve the effects of such *force majeure* and executes such plan within such timeframe. To the extent possible, each Party shall use reasonable efforts to minimize the duration of any *force majeure*.

11.6 Notices. Any notice or request required or permitted to be given under or in connection with this Agreement shall be deemed to have been sufficiently given if in writing and personally delivered or sent by certified mail (return receipt requested), facsimile transmission (receipt verified), or

overnight express courier service (signature required), prepaid, to the Party for which such notice is intended, at the address set forth for such Party below:

If to Regulus, addressed to:	Regulus Therapeutics Inc. 1896 Rutherford Road Carlsbad, California 92008 Attention: Chief Executive Officer Fax: 760-268-6868
with a copy to:	Isis Pharmaceuticals, Inc. 1896 Rutherford Road Carlsbad, California 92008 Attention: General Counsel Fax: 760-268-4922
	Cooley Godward Kronish LLP 4401 Eastgate Mall San Diego, CA 92121-1909 Attention: Thomas A. Coll Fax: 858-550-6420
	Alnylam Pharmaceuticals, Inc. 300 Third Street, 3rd Floor Cambridge, MA 02142 Attention: Vice President, Legal Fax: 617-551-8109
	WilmerHale 60 State Street Boston, MA 02109 Attention: Steven D. Singer, Esq. Fax: 617-526-5000
If to GSK, addressed to:	Attention: Business Development GlaxoSmithKline Greenford Road Greenford Middlesex UB6 0HE, United Kingdom Fax: +44 208 966 5371

with a copy to:	Attention: Vice President and Associate General Counsel, R&D Legal Operations GlaxoSmithKline301 Renaissance Boulevard Mail Code RN0220 King of Prussia, PA 19406 Telecopy: (610) 787-7084

or to such other address for such Party as it shall have specified by like notice to the other Party; provided that notices of a change of address shall be effective only upon receipt thereof. If delivered personally or by facsimile transmission, the date of delivery shall be deemed to be the date on which such notice or request was given. If sent by overnight express courier service, the date of delivery shall be deemed to be the next Business Day after such notice or request was deposited with such service. If sent by certified mail, the date of delivery shall be deemed to be the third Business Day after such notice or request was deposited with the U.S. Postal Service.

11.7 Export Clause. Each Party acknowledges that the laws and regulations of the United States restrict the export and re-export of commodities and technical data of United States origin. Each Party agrees that it will not export or re-export restricted commodities or the technical data of the other Party in any form without the appropriate United States and foreign government licenses.

11.8 Waiver. Neither Party may waive or release any of its rights or interests in this Agreement except in writing. The failure of either Party to assert a right hereunder or to insist upon compliance with any term or condition of this Agreement shall not constitute a waiver of that right or excuse a similar subsequent failure to perform any such term or condition. No waiver by either Party of any condition or term in any one or more instances shall be construed as a continuing waiver or subsequent waiver of such condition or term or of another condition or term.

11.9 Severability. If any provision hereof should be held invalid, illegal or unenforceable in any jurisdiction, the Parties shall negotiate in good faith a valid, legal and enforceable substitute provision that most nearly reflects the original intent of the Parties and all other provisions hereof shall remain in full force and effect in such jurisdiction and shall be liberally construed in order to carry out the intentions of the Parties hereto as nearly as may be possible. Such invalidity, illegality or unenforceability shall not affect the validity, legality or enforceability of such provision in any other jurisdiction.

11.10 Entire Agreement; Existing Collaboration. This Agreement, together with the Schedules and Exhibits hereto, and the relevant applicable cited provisions of the Existing

Collaboration, set forth all the covenants, promises, agreements, warranties, representations, conditions and understandings between the Parties and supersede and terminate all prior agreements and understanding between the Parties. There are no covenants, promises, agreements, warranties, representations, conditions or understandings, either oral or written, between the Parties other than as set forth herein and therein. No subsequent alteration, amendment, change or addition to this Agreement shall be binding upon the Parties hereto unless reduced to writing and signed by the respective authorized officers of the Parties. Notwithstanding the first sentence of this Section 11.10, except as explicitly stated in this Agreement, all the terms and conditions of the Existing Collaboration and the existing convertible promissory note by Regulus and its Founding Companies to GSK, dated April 24, 2008, shall remain unchanged and will continue in full force and effect.

11.11 Independent Contractors. Nothing herein shall be construed to create any relationship of employer and employee, agent and principal, partnership or joint venture between the Parties. Each Party is an independent contractor. Neither Party shall assume, either directly or indirectly, any liability of or for the other Party. Neither Party shall have the authority to bind or obligate the other Party and neither Party shall represent that it has such authority.

11.12 Headings. Headings used herein are for convenience only and shall not in any way affect the construction of or be taken into consideration in interpreting this Agreement.

11.13 Books and Records. Any books and records to be maintained under this Agreement by a Party or its Affiliates or Sublicensees shall be maintained in accordance with U.S. generally accepted accounting principles (or any successor standard) in the case of Regulus, and shall be maintained in accordance with International Financial Reporting Standards (IFRS) in the case of GSK, consistently applied, except that the same need not be audited.

11.14 Further Actions. Each Party shall execute, acknowledge and deliver such further instruments, and do all such other acts, as may be necessary or appropriate in order to carry out the expressly stated purposes and the clear intent of this Agreement.

11.15 Construction of Agreement. The terms and provisions of this Agreement represent the results of negotiations between the Parties and their representatives, each of which has been represented by counsel of its own choosing, and neither of which has acted under duress or compulsion, whether legal, economic or otherwise. Accordingly, the terms and provisions of this Agreement shall be interpreted and construed in accordance with their usual and customary meanings, and each of the Parties hereto hereby waives the application in connection with the interpretation and construction of this Agreement of any rule of law to the effect that ambiguous or conflicting terms or provisions contained in this Agreement shall be interpreted or construed against the Party whose attorney prepared the executed draft or any earlier draft of this Agreement.

11.16 Counterparts. This Agreement may be signed in counterparts, each and every one of which shall be deemed an original, notwithstanding variations in format or file designation which may result from the electronic transmission, storage and printing of copies of this Agreement from separate computers or printers. Facsimile signatures and signatures transmitted via PDF shall be treated as original signatures.

11.17 Compliance with Laws: Each Party shall and shall ensure that its Affiliates, Founding Companies, in the case of Regulus, and Sublicensees will, comply with all relevant laws and regulations in exercising their rights and fulfilling their obligations under this Agreement.

* - * - * - *

IN WITNESS WHEREOF, the Parties have caused this Agreement to be executed by their duly authorized representatives as of the Effective Date.

Regulus Therapeutics Inc.

By: */s/ Kleanthis G. Xanthopoulos*
Name: Kleanthis G. Xanthopoulos
Title: President and CEO
Date:

Glaxo Group Limited

By: */s/ Victoria Whyte*
Name: Victoria Whyte
Title: For and on behalf of the Wellcome Foundation Limited
Date:

LIST OF SCHEDULES AND EXHIBITS

EXHIBIT A — Definitions

EXHIBIT B — Representative List of Regulus Patents

EXHIBIT C — [***] Patent Rights

EXHIBIT D — Press Release

EXHIBIT E — [Intentionally Left Blank]

EXHIBIT F — Stanford Patents

EXHIBIT G — Relevant In-Licenses

DEFINITIONS

1. "**Acceptance**" means, with respect to an NDA filed for SPC-3649 or an SPC-3649 Product, (a) in the United States, the receipt by GSK, its Affiliates or Sublicensees of written notice from the FDA in accordance with 21 CFR 314.101(a)(2) that such NDA is officially "filed", (b) in the European Union, receipt by GSK of written notice of acceptance by the EMEA of such NDA for filing under the centralized European procedure in accordance with any feedback received from European Regulatory Authorities; provided, that if the centralized filing procedure is not used, then Acceptance shall be determined upon the acceptance of such NDA by the applicable Regulatory Authority in a Major Country in the EU, and (c) in Japan, receipt by GSK of written notice of acceptance of filing of such NDA from the Japanese Ministry of Health, Labour and Welfare ("**MHLW**").

2. "**Additional Third Party Agreement**" shall have the meaning assigned to such term in Section 5.6.2.

3. "**Affiliate**" shall mean any Person, whether *de jure* or *de facto*, which directly or indirectly through one (1) or more intermediaries controls, is controlled by or is under common control with another Person. A Person shall be deemed to "control" another Person if it (a) owns, directly or indirectly, beneficially or legally, at least fifty percent (50%) of the outstanding voting securities or capital stock (or such lesser percentage which is the maximum allowed to be owned by a Person in a particular jurisdiction) of such other Person, or has other comparable ownership interest with respect to any Person other than a corporation; or (b) has the power, whether pursuant to contract, ownership of securities or otherwise, to direct the management and policies of the Person. Notwithstanding the above, neither of the Founding Companies of Regulus shall be deemed an Affiliate of Regulus for the purposes of this Agreement under any circumstances.

4. "**Agreement**" shall have the meaning assigned to such term in the Recitals.

5. "**Agreement Term**" shall have the meaning assigned to such term in Section 10.1

6. "**Alnylam**" shall have the meaning assigned to such term in the Recitals.

7. "**Annual**" or "**Annually**" shall mean Calendar Year.

8. "**Bankruptcy Code**" shall have the meaning assigned to such term in Section 10.4.2.

9. "**Breaching Party**" shall have the meaning assigned to such term in Section 10.2.1.

10. "**Business Day**" shall mean any day other than a Saturday or Sunday on which banking institutions in both New York, New York and London, England are open for business.

11. "**Calendar Quarter**" shall mean a period of three (3) consecutive months ending on the last day of March, June, September, or December, respectively and will also include the period beginning on the Effective Date and ending on the last day of the calendar quarter in which the Effective Date falls.

12. "**Calendar Year**" shall mean a year of 365 days (or 366 days in a leap year) beginning on January 1st (or, with respect to 2010, the Effective Date) and ending December 31st, and so on year-by-year.

13. "**Claims**" shall have the meaning assigned to such term in Section 9.1.

14. "**Clinical Studies**" shall mean human studies designed to measure the safety, efficacy, tolerability and/or appropriate dosage of SPC-3649, as the context requires, including without limitation Phase 1 Clinical Trials, Phase 2 Clinical Trials (including any PoC Trial), Phase 3 Clinical Trials and any post-Regulatory Approval studies (such as Phase 4 Clinical Trials).

15. "**Collaboration Target**" shall have the meaning assigned to such term in the Existing Collaboration.

16. "**Combination Product**" shall have the meaning assigned to such term in the definition of "Net Sales" below.

17. "**Commercialize**" or "**Commercialization**" shall mean any and all activities directed to marketing, promoting, detailing, distributing, importing, having imported, exporting, having exported, selling or offering to sell an SPC-3649 Product following receipt of Regulatory Approval for such SPC-3649 Product.

18. "**Competitive Infringement**" shall have the meaning assigned to such term in Section 6.2.2.

19. "**Confidential Information**" shall have the meaning assigned to such term in Section 7.1.

20. "**Control**," "**Controls**," "**Controlled**" or "**Controlling**" shall mean the possession of the right (whether by ownership, license or otherwise) to assign, or grant a license, sublicense or other right, as provided for herein without violating the terms of any agreement or other arrangement with any Third Party or with any Founding Company of Regulus.

21. "**Develop**" or "**Development**" shall mean, with respect to a miRNA Compound or miRNA Therapeutic, any and all discovery, characterization, preclinical or clinical activity with respect to such miRNA Compound or miRNA Therapeutic, including human clinical trials conducted after Regulatory Approval of such miRNA Therapeutic to seek Regulatory Approval for additional indications for such miRNA Therapeutic.

22. "**Disclosing Party**" shall have the meaning assigned to such term in Section 7.1.

23. "**Effective Date**" shall have the meaning assigned to such term in the Recitals.

24. "**EMEA**" shall mean the European Medicines Evaluation Agency, and any successor entity thereto.

25. "**European Union**" or "**EU**" shall include Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Portugal, Spain, Sweden, United Kingdom, Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia, Slovenia, and any such other country or territory that may officially become part of the European Union after the Effective Date.

26. "**Executive Officers**" shall mean the Chief Executive Officer of Regulus (or a senior executive officer designated by such Person) and either the Chief Executive Officer or the Chairman of R&D at GSK (or another senior executive officer designated by such Persons).

27. "**Existing Collaboration**" shall have the meaning assigned to such term in the Recitals.

28. "**FDA**" shall mean the U.S. Food and Drug Administration, and any successor entity thereto.

29. "**Field**" shall mean the treatment and/or prophylaxis of hepatitis C virus.

30. "**First Commercial Sale**" means, with respect to an SPC-3649 Product in a country in the Territory, the first sale, transfer or disposition for value by GSK, its Affiliates or Sublicensees to an end user of an SPC-3649 Product in such country; provided, that, the following shall not constitute a First Commercial Sale: (a) any sale to an Affiliate, Founding Company or Sublicensee unless the Affiliate, Founding Company or Sublicensee is the last entity in the distribution chain the SPC-3649 Product, (b) any use of SPC-3649 or an SPC-3649 Product in Clinical Studies, pre-clinical studies or other research or development activities, or disposal or transfer of SPC-3649 or an SPC-3649 Product for a bona fide charitable purpose, (c) compassionate use, (d) so called "treatment IND sales" and "named patient sales," and (e) use under the ATU system in France and/or the International Pharmi system in Europe.

31. "**Founding Company**" shall have the meaning assigned to such term in the Recitals.

32. "**Founding Company Patents**" shall mean, with respect to each Founding Company,

(a) all Patent Rights Controlled by such Founding Company on the Effective Date that claim:

(i) miRNA Compounds or miRNA Therapeutics in general,

(ii) specific miRNA Compounds or miRNA Therapeutics,

(iii) [***] of miRNA Compounds or miRNA Therapeutics,

(iv) [***] by which a miRNA Antagonist directly prevents the production of the specific miRNA, or

(v) [***], by modulating one or more miRNAs;

provided, however, that in each case of (a) and (b), (x) for any such Patent Rights that include [***] (as defined in the Regulus License Agreement), the provisions of Section 2.4 of the Regulus License Agreement will govern whether, with respect to a Patent Right licensed under an Optional In-License (as defined in the Regulus License Agreement) or as an Additional Right (as defined in the Regulus License Agreement), such Patent Right will be included as a Founding Company Patents, and (y) Founding Company Patents do not include [***].

33. **"Garching Agreement"** means the Amended License Agreement dated October 18, 2004 among Max Plank Innovation GmbH (formerly Garching Innovation GmbH), Isis and Alnylam

34. "**GSK**" shall have the meaning assigned to such term in the Recitals.

35. "**IND**" shall mean any investigational new drug application filed with the FDA pursuant to Part 312 of Title 21 of the U.S. Code of Federal Regulations, including any amendments thereto. References herein to IND shall include, to the extent applicable, any comparable filing(s) outside the U.S. (such as a Clinical Trial Application in the European Union).

36. "**Indemnitee**" shall have the meaning assigned to such term in Section 9.3.

37. "**Initiation**" shall mean, with respect to any human Clinical Studies set forth in Section 6.4, the first dosing of the first patient or subject in such study.

38. "**Isis**" shall have the meaning assigned to such term in the Recitals.

39. "**Know-How**" shall mean any information, inventions, trade secrets or technology (excluding Patent Rights), whether or not proprietary or patentable and whether stored or transmitted in oral, documentary, electronic or other form. Know-How includes ideas, concepts, formulas, methods, procedures, designs, compositions, plans, documents, data, discoveries, developments, techniques, protocols, specifications, works of authorship, biological materials, and any information relating to research and development plans, experiments, results, compounds, therapeutic leads, candidates and products, clinical and preclinical data, clinical trial results, and Manufacturing information and plans.

40. "**Losses**" shall have the meaning assigned to such term in Section 9.1.

41. "**Major Country**" shall mean any of the following countries: the [***].

42. "**Manufacture**" or "**Manufacturing**" shall mean any activity involved in or relating to the manufacturing, quality control testing (including in-process, release and stability testing), releasing or packaging, for pre-clinical, clinical or commercial purposes, of a miRNA Compound or a miRNA Therapeutic.

43. "**Milestone Event**" shall have the meaning assigned to such term in Section 5.4.

44. "**miRNA**" shall mean a structurally defined functional RNA molecule usually between [***] and [***] nucleotides in length, which is derived from genetically-encoded non-coding RNA which is predicted to be processed into a hairpin RNA structure that is a substrate for the double-stranded RNA-specific ribonuclease Drosha and subsequently is predicted to serve as a substrate for the enzyme Dicer, a member of the RNase III enzyme family; including, without limitation, those miRNAs exemplified in miRBase (http://microrna.sanger.ac.uk/). To the extent [***] for purposes of this Agreement; provided, however, that nothing contained herein shall require any Party hereto to expand this definition.

45. "**miRNA Antagonist**" shall mean a single-stranded oligonucleotide (or a single stranded analog thereof) that [***] interfere with or inhibit a particular miRNA. For purposes of clarity, the definition of "miRNA Antagonist" is not intended to include oligonucleotides that function predominantly through [***].

46. "**miRNA Compound**" shall mean a compound consisting of a miRNA Antagonist. For purposes of clarity, miRNA Compound [***].

47. "**miRNA Mimic**" shall mean a double-stranded or single-stranded oligonucleotide or analog thereof with a substantially similar base composition as a particular miRNA and which [***] mimic the activity of such miRNA.

48. "**miRNA Precursor**" shall mean a transcript that originates from a genomic DNA and that contains, but not necessarily exclusively, a non-coding, structured RNA comprising one or more mature miRNA sequences, including, without limitation, (a) polycistronic transcripts comprising more than one miRNA sequence, (b) miRNA clusters comprising more than one miRNA sequence, (c) pri-miRNAs, and/or (d) pre-miRNAs.

49. "**miRNA Precursor Antagonist**" shall mean a single-stranded oligonucleotide (or a single stranded analog thereof) that [***] bind to a miRNA Precursor to prevent the production of one or more miRNAs. For purposes of clarity, the definition of "miRNA Precursor Antagonist" is not intended to include oligonucleotides that function predominantly through the RNAi mechanism of action or the RNase H mechanism of action.

50. "**miRNA Therapeutic**" shall mean a therapeutic product having one or more miRNA Compounds as an active ingredient(s).

51. "**NDA**" shall mean a New Drug Application (as more fully defined in 21 C.F.R. 314.5 et seq. or its successor regulation) and all amendments and supplements thereto filed with the FDA, or the equivalent application filed with any equivalent agency or governmental authority outside the U.S. (including any supra-national agency such as the EMEA in the EU).

52. "**Net Sales**" shall mean, with respect to any SPC-3649 Product, the gross invoiced sales of SPC-3649 Product sold by GSK, its Affiliates or Sublicensees (in each case, the "Selling Party"), in finished product form, packaged and labeled for sale, under this Agreement in arm's length sales to Third Parties, less the following deductions which are actually incurred, allowed, paid, accrued or specifically allocated to the Third Party customer by the Selling Party, to the

extent actually taken by such Third Party customer, on such sales for: (a) [***] trade, quantity, and cash discounts; (b) [***] credits, rebates and chargebacks (including those to [***] including [[***], and allowances or credits to customers on account of [***] or on account of [***] affecting such SPC-3649 Product; (c) [***] charges relating to such SPC-3649 Product, including [***] thereto; (d) [***] directly linked to the sales of such SPC-3649 Product to the extent included in the gross amount invoiced; (e) the lesser or [***] of Net Sales or [***]; (f) [***] allowed or paid to [***] employed by the Selling Party; and (g) any other items actually deducted from gross invoiced sales amounts as reported by such Party in its financial statements in accordance with, in the case of GSK's Net Sales, the International Financial Reporting Standards, applied on a consistent basis, and, in the case of Regulus' Net Sales, the U.S. generally accepted accounting principles applied on a consistent basis.

Net Sales will not include any transfer or sale between or among a Party and any of its Affiliates or Founding Companies or direct Sublicensees.

SPC-3649 Product provided to patients for [***] will not be included in Net Sales.

In the event SPC-3649 is sold as part of a Combination Product (as defined below), the Net Sales from the SPC-3649, for the purposes of determining royalty payments, will be determined by multiplying the Net Sales (as determined without reference to this paragraph) of the Combination Product, by the fraction, A/A+B, where A is the [***] price (determined substantially in accordance with the above) of the SPC-3649 when sold separately in finished form and B is the [***] price (determined substantially in accordance with the above) [***] in the Combination Product when sold separately in finished form, each during the applicable royalty period or, if sales of all compounds did not occur in such period, then in the most recent royalty reporting period in which sales of all occurred. In the event that such [***] price cannot be determined for both the SPC-3649 and all other therapeutically active pharmaceutical compounds included in the Combination Product, Net Sales for the purposes of determining royalty payments will be calculated as above, but the [***] price in the above equation will be replaced by a good faith estimate of the [***] for which no such price exists. As used above, the term "Combination Product" shall mean any pharmaceutical product which consists of SPC-3649 and other therapeutically active pharmaceutical compound(s).

53. "**Non-breaching Party**" shall have the meaning assigned to such term in Section 10.2.1.

54. "**Party**" or "**Parties**" shall have the meaning assigned to such term in the Recitals.

55. "**Patent Rights**" shall mean (a) patent applications (including provisional applications and for certificates of invention), (b) any patents issuing from such patent applications (including certificates of invention), (c) all patents and patent applications based on, corresponding to, or claiming the priority date(s) of any of the foregoing, and (c) any substitutions, extensions (including supplemental protection certificates), registrations, confirmations, reissues, divisionals, continuations, continuations-in-part, re-examinations, renewals and foreign counterparts thereof.

56. "**Payee**" shall mean the Party to whom milestone payments or royalties are payable hereunder.

57. "**Payor**" shall mean GSK and, with respect to milestone payments, GSK.

58. "**Pending Claim**" means a claim within any patent application in the Regulus Patents that has not been cancelled, withdrawn, or abandoned. For purposes of clarity, if any Pending Claim of a patent application subsequently issues, such claim shall be deemed to qualify as a Valid Claim (as defined herein).

59. "**Person**" shall mean any corporation, limited or general partnership, limited liability company, joint venture, trust, unincorporated association, governmental body, authority, bureau or agency, any other entity or body, or an individual.

60. "**Phase 1 Clinical Trial**" means a Clinical Study in any country, the principal purpose of which is a preliminary determination of safety in healthy individuals or patients that would satisfy the requirements of 21 CFR 312.21(a), or an equivalent clinical study required by a Regulatory Authority in a jurisdiction outside of the United States.

61. "**Phase 2 Clinical Trial**" means a Clinical Study conducted in any country that is intended to explore a variety of doses, dose response and duration of effect to generate initial evidence of clinical safety and activity in a target patient population, that would satisfy the requirements of 21 CFR 312.21(b), or an equivalent clinical study required by a Regulatory Authority in a jurisdiction outside of the United States.

62. "**Phase 3 Clinical Trial**" means a Clinical Study in any country performed after preliminary evidence of efficacy has been obtained, which if successful, would provide sufficient evidence of the safety and efficacy of a product to support a Regulatory Approval, and that would satisfy the requirements of 21 CFR 312.21(c), or an equivalent clinical study required by Regulatory Authority in a jurisdiction outside of the United States.

63. "**Phase 4 Clinical Trial**" means a Clinical Study in any country which is conducted after Regulatory Approval of a product has been obtained from an appropriate Regulatory Authority, consisting of trials conducted voluntarily for enhancing marketing or scientific knowledge of an approved indication and trials conducted due to request or requirement of a Regulatory Authority.

64. "**PoC Trial**" shall mean the first human in-patient study designed to provide evidence of efficacy, safety and tolerability of SPC-3649 or an SPC-3649 Product.

65. "**PoC Trial Reports**" shall mean a reasonably complete data package containing all material analysis, results and clinical data or any related material correspondence or information received from or sent to any Regulatory Authority relating to SPC-3649 or an SPC-3649 Product.

66. "**Proceeding**" shall mean an action, suit or proceeding.

67. "**Prosecution and Maintenance**" or "**Prosecute and Maintain**" shall mean, with regard to a Patent Right, the preparing, filing, prosecuting and maintenance of such Patent Right, as well as handling re-examinations, reissues, and requests for patent term extensions with respect to such Patent Right, together with the conduct of interferences, the defense of oppositions and other similar proceedings with respect to the particular Patent. For clarification, "Prosecution and Maintenance" or "Prosecute and Maintain" shall not include any other enforcement actions taken with respect to a Patent Right.

68. "**Receiving Party**" shall have the meaning assigned to such term in Section 7.1.

69. "**Regulatory Approval**" shall mean any and all approvals (including price and reimbursement approvals, if required prior to sale in the applicable jurisdiction), licenses, registrations, or authorizations of any country, federal, supranational, state or local regulatory agency, department, bureau or other government entity that are necessary for the manufacture, use, storage, import, transport and/or sale of SPC-3649 or an SPC-3649 Product in the applicable jurisdiction.

70. "**Regulatory Authority**" or "**Regulatory Authorities**" shall mean the FDA in the U.S., and any health regulatory authority(ies) in any country in the Territory that is a counterpart to the FDA and holds responsibility for granting Regulatory Approval for SPC-3649 or an SPC-3649 Product in such country, and any successor(s) thereto.

71. "**Regulus**" shall have the meaning assigned to such term in the Recitals.

72. "**Regulus License Agreement**" means the Amended and Restated License and Collaboration Agreement dated January 1, 2009 among Regulus, Isis and Alnylam.

73. "**Regulus Patents**" shall mean:

(a) all Founding Company Patents Controlled by Regulus or any of its Affiliates as of the Effective Date and/or after the Effective Date and having an earliest priority date of no later than the Effective Date, including without limitation those listed on Exhibit B,

(b) all Patent Rights, other than Founding Company Patents, Controlled by Regulus or any of its Affiliates as of the Effective Date and/or after the Effective Date and having an earliest priority date of no later than the Effective Date, including without limitation the Patent Rights listed on Exhibit F,

in each case, that are necessary to Development, Manufacture or Commercialize SPC-3649 in the Field: provided, however, that in each case of (a) through (b), (y) for any Patent Right that is the subject of an Additional Third Party Agreement, the provisions of Section 5.6.2 will govern whether such Patent Right will be included as a Regulus Patent hereunder, and (z) unless the Parties enter into a Tuschl 3 Sublicense under Section 2.1 of this Agreement , Regulus Patents will exclude the Tuschl 3 Patents.

74. "**Royalty Tail Period**" shall have the meaning assigned to such term in Section 5.5.2.

75. "**Santaris**" shall mean Santaris Pharma A/S.

76. "**Santaris Agreement**" shall mean that certain Research and Development Collaboration and License Agreement between SmithKline Beecham Corporation d/b/a/ GlaxoSmithKline and Santaris, dated December 18, 2007.

77. "**SEC**" shall mean the U.S. Securities and Exchange Commission.

78. "**Selling Party**" shall have the meaning assigned to such term in Section 52 .

79. "**SPC-3649**" shall mean (a) the proprietary Santaris compound known on the Effective Date as SPC-3649, and (b) any and all salts, crystalline and amorphous forms, and solvates (including hydrates) thereof. The sequence and chemistry of SPC-3649 is described in [***].

80. "**SPC-3649 Product**" means any product that includes SPC-3649 as an active ingredient, or includes SPC-3649 in any base form, salt form, prodrug, ester, crystalline polymorph, hydrate or solvate thereof, whether or not as the sole active ingredient and in any dosage, form or formulation, sold by GSK, its Affiliates or Sublicensees, in finished product form, packaged and labeled for sale. Unless otherwise indicated by context, "Product" or "SPC-3649 Product" includes Combination Products.

81. "**SPC-3649 Rights**" shall have the meaning assigned to such term in Section 3.2(a).

82. "**Stanford**" means The Board of Trustees of the Leland Stanford Junior University.

83. "**Stanford License Agreement**" means the Co-Exclusive License Agreement dated August 31, 2005 among Stanford and the Founding Companies (as assigned by Isis to Regulus on July 13, 2009).

84. "**Stanford Patent(s)**" means any Patent Right licensed under the Stanford License Agreement. A list of the Stanford Patents as of the Effective Date is attached hereto under Exhibit F.

85. "**Sublicensee**" shall mean a Third Party or Founding Company to whom a Party or its Affiliates or Sublicensees has granted a sublicense or license under any Regulus Patents, licensed to such Party in accordance with the terms of this Agreement.

86. "**Territory**" shall mean all of the countries and territories of the world.

87. "**Third Party**" shall mean any Person other than Regulus or GSK or an Affiliate of Regulus or GSK or a Founding Company of Regulus.

88. "**Third Party License Pass-Through Costs**" shall mean, (a) with respect to Regulus, the licensing costs and payments that Regulus owes to Third Parties, but excluding any costs and payments of any kind owed by Regulus to [***], or (b) with respect to GSK, the

licensing costs and payments that GSK owes to Third Parties, in each case as a result of the practice of intellectual property licensed from such Third Parties in the Development, Manufacture and/or Commercialization of SPC-3649 hereunder, including, without limitation, all [***] payments. For clarity, any such costs and payments owed to Third Parties by a Party (x) shall only include the share of such costs and payments which is [***], and not by any of its Affiliates or by Regulus, [***], as applicable (although, for clarity, if such costs and payments are paid by [***], as applicable, solely in order for such [***] to the relevant Third Party in those situations in which (i) GSK is a sublicensee of such Third Party, through its Affiliate, then such costs and payments shall

be [***], or (ii) Regulus is a sublicensee of such Third Party through its Affiliate or Founding Company, then such costs and payments shall be [***], in each case subject to the following clause (y)), and (y) shall only include any such costs and payments to the [***].

89. "**Third Party and Founding Company-Originated Rights and Obligations**" shall mean the rights of, and any limitations, restrictions or obligations imposed by, (a) Founding Companies pursuant to the Regulus License Agreement and (b) Third Parties pursuant to (i) the contracts assigned to Regulus pursuant to Section 2.1 of the Regulus License Agreement, including but not limited to the Stanford License Agreement, [***] (as defined in the Regulus License Agreement), [***] (as defined in the Regulus License Agreement), [***] (as defined in the Regulus License Agreement), [***] (each as defined in the Regulus License Agreement) [***]

90. "**Total License Pass-Through Costs**" shall mean the licensing costs and payments that [***] as a result of the practice of intellectual property licensed from any such [***] in the Development, Manufacture and/or Commercialization of SPC-3649 or an SPC-3649 Product hereunder, including, without limitation, all upfront fees, annual payments, milestone payments and royalty payments. For clarity, any such costs and payments (a) shall only include the share of such costs and payments which is [***], and not by any of [***] (although, for clarity, if such costs and payments are paid [***] solely in order for [***] to the relevant Third Party in those situations in which [***], of such Third Party, then such costs and payments shall be [***], subject to clause (b)), and (b) shall only include any such costs and payments to the [***].

91. "[***] **Patents**" means all Patent Rights licensed by Isis and/or Alnylam under the License Agreement among [***], Isis and Alnylam dated [***], as amended. A representative list of the [***] Patents as of the Effective Date is attached hereto under Exhibit C.

92. "[***] **Sublicense**" will have the meaning assigned to such term in Section 2.1.

93. "**United States**" or "**U.S.**" shall mean the fifty states of the United States of America and all of its territories and possessions and the District of Columbia.

94. "**Upfront Payment**" shall have the meaning assigned to such term in Section 5.1.

95. "**Valid Claim**" means a claim within an issued Patent in the Regulus Patents that has not expired, lapsed, been cancelled or abandoned, and that has not been dedicated to the public, disclaimed or been revoked, cancelled or held unenforceable or invalid by a decision of a court or governmental administrative agency of competent jurisdiction from which no appeal can be taken, or with respect to which an appeal is not taken within the time allowed for appeal, and that has not been disclaimed or admitted to be invalid or unenforceable including through opposition, re-examination, reissue, disclaimer or otherwise.

96. "**Withholding-Free Payments**" means the [***] and [***] payments payable to Regulus under Sections [***] and [***] of this Agreement.

EXHIBIT B

Representative List of Regulus Patents as of the Effective Date

[***]

EXHIBIT C

[***] Patents as of the Effective Date

[***]

EXHIBIT D

Press Release

Regulus Therapeutics and GlaxoSmithKline Establish New Collaboration to Develop and Commercialize microRNA Therapeutics Targeting miR-122

- miR-122 Represents a Novel "Host Factor" Strategy for Treatment of Hepatitis C Infection —

- Further Demonstration of Regulus Leadership in microRNA Science, Technology and Intellectual Property -

Carlsbad, CA., February 24, 2010 — Regulus Therapeutics Inc. today announced the establishment of a new collaboration with GlaxoSmithKline (GSK) to develop and commercialize microRNA therapeutics targeting microRNA-122 in all fields with Hepatitis C Viral infection (HCV) as the lead indication. Under the terms of the new collaboration, Regulus will receive additional upfront and early-stage milestone payments with the potential to earn more than $150 million in miR-122-related combined payments, and tiered royalties up to double digits on worldwide sales of products.

"This new collaboration with GSK demonstrates the clear scientific leadership that Regulus has established in advancing a whole new frontier of pharmaceutical research. microRNA therapeutics target the pathways of human diseases, not just single disease targets, and hold considerable promise as novel therapies across a broad range of unmet medical needs," said Kleanthis G. Xanthopoulos, Ph.D., President and Chief Executive Officer of Regulus. "It also further validates Regulus' microRNA product platform built on fundamental biology of human diseases and intellectual property, and also extends the therapeutic scope of our existing collaboration formed with GSK in 2008. Furthermore, the funding from this alliance supports Regulus' efforts in advancing high impact, novel medicines based on microRNA biology to patients."

The collaboration provides GSK with access to Regulus' comprehensive and robust intellectual property estate. Regulus exclusively controls patent rights covering miR-122 antagonists and their use as HCV therapeutics in the United States, Europe, and Japan, including but not limited to the patent families which encompass: the 'Sarnow' patent pertaining to the method of use of anti-miR-122 to inhibit HCV replication, the 'Esau' patent application claiming the use of anti-miRs targeting miR-122 as inhibitory agents, the 'Tuschl III' patent claiming composition of matter for miR-122 and complementary oligonucleotides, and the 'Manoharan' patent claiming antagomirs, including antagomirs targeting miR-122.

miR-122 is a liver-expressed microRNA that has been shown to be a critical endogenous "host factor" for the replication of HCV, and anti-miRs targeting miR-122 have been shown to block HCV infection (Jopling *et al.* (2005) *Science* 309, 1577-81). In earlier work, scientists at Alnylam and Isis demonstrated the ability to antagonize miR-122 *in vivo* using chemically modified single-stranded anti-miR oligonucleotides. Further, work by Regulus scientists and collaborators showed that inhibiting miR-122 results in significant inhibition of HCV replication in human liver cells, suggesting that antagonism of miR-122 may comprise a novel "host factor"

therapeutic strategy. Regulus scientists have shown in multiple preclinical studies a robust HCV antiviral effect following inhibition of miR-122. Regulus plans to identify a clinical development candidate in the second half of 2010 and file an investigational new drug (IND) application in 2011.

About microRNAs

The discovery of microRNA in humans is one of the most exciting scientific breakthroughs in the last decade. microRNAs are small RNA molecules, typically 20 to 25 nucleotides in length, that do not encode proteins but instead regulate gene expression. Nearly 700 microRNAs have been identified in the human genome, and more than one-third of all human genes are believed to be regulated by microRNAs. As a single microRNA can regulate entire networks of genes, these new molecules are considered the master regulators of the genome. microRNAs have been shown to play an integral role in numerous biological processes including the immune response, cell-cycle control, metabolism, viral replication, stem cell differentiation and human development. Many microRNAs are conserved across multiple species indicating the evolutionary importance of these molecules as modulators of critical biological pathways. Indeed, microRNA expression or function has been shown to be significantly altered in many disease states, including cancer, heart failure and viral infections. Targeting microRNAs opens the possibility of a novel class of therapeutics and a unique approach to treating disease by modulating entire biological pathways.

About Hepatitis C Virus (HCV)

HCV infection is a disease with an estimated prevalence of 170 million patients worldwide, with more than 3 million patients in the United States. HCV shows significant genetic variation in worldwide populations due to its frequent rates of mutation and rapid evolution. There are six genotypes of HCV, with several subtypes within each genotype, which vary in prevalence across the different regions of the world. The response to treatment varies from individual to individual underscoring the inadequacy of existing therapies and highlights the need for combination therapies that not only target the virus but endogenous "host factors" as well. Strategies that include the Regulus miR-122 antagonist as part of emerging combination therapies to shorten duration of treatment and interferon use, improve the safety profile and sustained virologic response (SVR), increase the barrier to drug resistance, and address difficult-to-treat genotypes hold significant potential to expand the limited therapies available to physicians treating HCV patients.

About Regulus Therapeutics Inc.

Regulus Therapeutics is a biopharmaceutical company leading the discovery and development of innovative new medicines based on microRNAs. Regulus is targeting microRNAs as a new class of therapeutics by working with a broad network of academic collaborators and leveraging oligonucleotide drug discovery and development expertise from its founding companies Alnylam Pharmaceuticals (*Nasdaq:ALNY*) and Isis Pharmaceuticals (*Nasdaq:ISIS*). Regulus is advancing microRNA therapeutics towards the clinic in several areas including hepatitis C infection, cardiovascular disease, fibrosis, oncology, immuno-inflammatory diseases, and metabolic diseases. Regulus' intellectual property estate contains both the fundamental and core patents in the field as well as over 600 patents and more than 300 pending patent applications pertaining primarily to chemical modifications of oligonucleotides targeting microRNAs for therapeutic

applications. In 2008, Regulus entered into a major alliance with GlaxoSmithKline to discover and develop microRNA therapeutics for immuno-inflammatory diseases. For more information, visit www.regulusrx.com.

Forward-Looking Statements

This press release includes forward-looking statements regarding the future therapeutic and commercial potential of Regulus', Alnylam's, and Isis' business plans, technologies and intellectual property related to microRNA therapeutics being discovered and developed by Regulus, including statements regarding expectations around the relationship between GSK and Regulus. Any statement describing Regulus', Alnylam's, and Isis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are

described as such parties' goals. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such products. Such parties' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause their results to differ materially from those expressed or implied by such forward-looking statements. Although these forward-looking statements reflect the good faith judgment of the management of each such party, these statements are based only on facts and factors currently known by Regulus', Alnylam's, and Isis' management as the case may be. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Regulus', Alnylam's, and Isis' programs are described in additional detail in Alnylam's and Isis' annual reports on Form 10-K for the year ended December 31, 2008, and their most recent quarterly reports on Form 10-Q which are on file with the SEC. Copies of these and other documents are available from Alnylam or Isis.

EXHIBIT E

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EXHIBIT F

Stanford Patents as of the Effective Date

[***]

EXHIBIT G

Third Party In-Licenses

[***]

EXHIBIT H

[***] License Terms

The following is a summary of material terms that would apply to a license under [***] Patents (as set forth in Appendix 1) for SPC-3649, in relation to SPC-3649 Rights. Terms used herein and not otherwise defined shall have the meaning assigned to such term in the Agreement.

Licensor	Regulus Therapeutics Inc.
Licensee	Santaris A/S
Field	The treatment and/or prophylaxis of hepatitis C virus
Territory	Worldwide
Santaris Option	Santaris' option (the "Santaris Option") to take an exclusive license from Regulus under the [***] Patents to develop and commercialize only SPC-3649 within the Field. The Santaris Option can be exercised by Santaris: 1. if after GSK takes a license to SPC-3649 it subsequently ceases development of SPC-3649 and returns rights to SPC-3649 to Santaris. The Santaris Option would expire sixty (60) days following the event above.
Up-front Payment	[***] [***]] however if GSK has taken license to SPC-3649 and made the corresponding $[***] payment to Regulus following completion of the PoC Trial, then this payment would be waived.
Milestones to Regulus	Santaris would pay the following milestones to Regulus, based upon the achievement of the milestone event by SPC-3649:

Milestone Event	Milestone Payment* US$Million ("m")
[***]	[***]
[***]	[***]
[***]	[***]

[***]	[***]
[***]	[***]
[***]	[***]

*Each milestone will be paid only once upon the first achievement of the Milestone Event by SPC-3649. For clarity, if GSK had paid a milestone, then the milestone would not be payable a second time by Santaris.

†Such milestone will only be payable if, at the time such milestone is achieved there is a Valid Claim within the [***] Patents, which covers [***]; provided, however, that if there is no Valid Claim at the time of such Milestone Event, then (a) Santaris must pay to Regulus [***] of such milestone payment upon the First Commercial Sale of an SPC-3649 Product in any country in the [***]; and (b) if a Pending Claim within the [***] Patents issues such that it is a Valid Claim in the [***] prior to the [***] anniversary of the date of the First Commercial Sale described in clause (a) above, then Santaris will pay Regulus the remaining [***] of such milestone within thirty (30) days of receipt by Santaris of an invoice sent from Regulus on or after the date of the issuance of the applicable Pending Claim.

“Clinical Studies” shall mean human studies designed to measure the safety, efficacy, tolerability and/or appropriate dosage of SPC-3649, as the context requires, including without limitation Phase 1 Clinical Trials, Phase 2 Clinical Trials (including any PoC Trial), Phase 3 Clinical Trials and any post-Regulatory Approval studies (such as Phase 4 Clinical Trials).

“First Commercial Sale” means, with respect to an SPC-3649 Product in a country in the Territory, the first sale, transfer or disposition for value by Santaris, its Affiliates or Sublicensees to an end user of an SPC-3649 Product in such country; provided, that, the following shall not constitute a First Commercial Sale: (a) any sale to an Affiliate, Founding Company or Sublicensee unless the Affiliate, Founding Company or Sublicensee is the last entity in the distribution chain the SPC-3649 Product, (b) any use of SPC-3649 or an SPC-3649 Product in Clinical Studies, pre-clinical studies or other research or development activities, or disposal or transfer of SPC-3649 or an SPC-3649 Product for a bona fide charitable purpose, (c) compassionate use, (d) so called “treatment IND sales” and “named patient sales,” and (e) use under the ATU system in France and/or the International Pharmi system in Europe.

“Pending Claim” means a claim within any patent application in the [***] Patents that has not been cancelled, withdrawn, or abandoned. For purposes of clarity, if any Pending Claim of a patent application subsequently issues, such claim shall be deemed to qualify as a Valid Claim.

“Regulatory Approval” shall mean any and all approvals (including price and reimbursement approvals, if required prior to sale in the applicable jurisdiction), licenses, registrations, or authorizations of any country, federal, supranational, state or local regulatory agency,

department, bureau or other government entity that are necessary for the manufacture, use, storage, import, transport and/or sale of SPC-3649 or an SPC-3649 Product in the applicable jurisdiction.

“SPC-3649 Product” means any product that includes SPC-3649 as an active ingredient, or includes SPC-3649 in any base form, salt form, prodrug, ester, crystalline polymorph, hydrate or solvate thereof, whether or not as the sole active ingredient and in any dosage, form or formulation, sold by Santaris, its Affiliates or Sublicensees, in finished product form, packaged and labeled for sale. Unless otherwise indicated by context, “Product” or “SPC-3649 Product” includes Combination Products.

“Valid Claim” means a claim within an issued Patent in the [***] Patents that has not expired, lapsed, been cancelled or abandoned, and that has not been dedicated to the public, disclaimed or been revoked, cancelled or held unenforceable or invalid by a decision of a court or governmental administrative agency of competent jurisdiction from which no appeal can be taken, or with respect to which an appeal is not taken within the time allowed for appeal, and that has not been disclaimed or admitted to be invalid or unenforceable including through opposition, re-examination, reissue, disclaimer or otherwise.

Royalties to Regulus

Santaris will pay to Regulus royalties on Annual worldwide Net Sales of any SPC-3649 Product sold by Santaris, its Affiliates or Sublicensees (“Santaris Patent Royalty”) during a calendar year, on a country-by-country basis, in the Field in the countries of the Territory in which there is a Valid Claim in the Field within the [***] Patents, which [***], in the amounts as follows:

Annual Worldwide Net Sales (U.S. $ Million) of SPC-3649 Product per Calendar Year US$Million (“m”)	**Applicable Royalty Rate**
up to $1000m	[***]%
$1000m up to $2000m	[***]%
$2000m up to $3000m	[***]%
> $3000m	[***]%

The royalty rates in the table above are incremental rates, which apply only for the respective increment of Annual worldwide Net Sales described in the Annual worldwide Net Sales column. Thus, once a total Annual worldwide Net

Sales figure is achieved for the year, the

royalties owed on any lower tier portion of Annual worldwide Net Sales are not adjusted up to the higher tier rate.

Royalty Adjustment. If there are no Valid Claims within the [***] Patents that claim [***] SPC-3649 Product sold in a particular country, the Santaris Patent Royalty set forth above shall be reduced to [***] of the Santaris Patent Royalty rates above in such countries where a Pending Claim within the [***] Patents claims [***] has not yet been issued. For the avoidance of doubt, for such Pending Claims, Santaris shall pay Regulus [***] of the Santaris Patent Royalty set forth in the table above, and shall pay the remaining [***] of the Santaris Patent Royalty into an escrow account, until such time as a Valid Claim within the [***] Patents issues that covers the [***] being sold in the country of sale, provided that such Valid Claim must issue within [***] years of date of First Commercial Sale of an SPC-3649 Product (the "Royalty Tail Period"). In the event such Valid Claim issues during the Royalty Tail Period, (i) the escrow account and any interest thereon shall be paid to Regulus and (ii) Santaris will pay the full Santaris Patent Royalty in such countries starting only from the date of such issuance of the Valid Claim and shall not owe any Santaris Patent Royalty in such countries for any preceding period. In the event that no such Valid Claim issues during the Royalty Tail Period, then the escrowed amounts and any interest thereon shall be returned to Santaris and any obligations Santaris may have had with respect to the Pending Claims shall cease. If Santaris maintains sole control over such escrow account then Santaris shall be solely responsible for the costs and expenses associated with maintaining such escrow account, otherwise Santaris and Regulus shall be mutually responsible for the costs and expenses associated with maintaining such escrow account; provided, that the Parties must mutually agree (such agreement not to be unreasonably withheld) before taking any action that would cause Santaris to lose sole control of such escrow account. If a Valid Claim within the [***] Patents that [***] issues after the Royalty Tail Period, then Santaris will pay Regulus the full Santaris Patent Royalty in such countries starting only from the date of such issuance of the Valid Claim and shall not owe any Santaris Patent Royalty in such countries for any preceding period.

Prosecution and Maintenance of Sarnow Patents	At Regulus' expense, Regulus shall (but shall not be obligated to) control and be responsible for all aspects of the Prosecution, Maintenance, enforcement and defense of all Sarnow Patents
No Challenge	Santaris covenants to Regulus that pursuant to the Santaris Option to take a license to the [***] Patents, that during the term of the Santaris Option and any license agreement granted thereunder, solely with respect to claims within the Regulus Patent Rights to the [***] Patents that are to be included in the license to be granted to Santaris pursuant to the terms set forth in this Exhibit H, Santaris, its Affiliates or

Sublicensees will not, in the U.S. or any other Major Country, (a) commence or otherwise voluntarily determine to participate in (other than as may be necessary or reasonably required to assert a cross-claim or a counter-claim or to respond to a court request or order or administrative law request or order) any action or proceeding, challenging or denying the validity of any claim within an issued patent or patent application within the [***] Patents, or (b) direct, support or actively assist any other Person (other than as may be necessary or reasonably required to assert a cross-claim or a counter-claim or to respond to a court request or order or administrative law request or order) in bringing or prosecuting any action or proceeding challenging or denying the validity of any claim within an issued patent or patent application within the [***] Patents. For purposes of clarification, any breach of these terms will be a material breach of the license granted to Santaris, and will be grounds for termination by Regulus of the license.

"Patent Rights" shall mean (a) patent applications (including provisional applications and for certificates of invention), (b) any patents issuing from such patent applications (including certificates of invention), (c) all patents and patent applications based on, corresponding to, or claiming the priority date(s) of any of the foregoing, and (c) any substitutions, extensions (including supplemental protection certificates), registrations, confirmations, reissues, divisionals, continuations, continuations-in-part, re-examinations, renewals and foreign counterparts thereof.

Research Plan	If Santaris exercises the Santaris Option to take a license to the [***] Patents, Regulus and Santaris will jointly prepare a research plan for SPC-3649; provided, that (i) Santaris shall not be required to share with Regulus or any confidential information; and (ii) Santaris will have the sole decision making authority with respect to such research plan.
Stanford License Considerations	With respect to the sublicense granted by Regulus under the [***] Patents, Santaris acknowledges and agrees that (a) such sublicense is subject and subordinate to the terms and conditions of the Stanford License Agreement, (b) Stanford is a third party beneficiary to this Agreement as it relates to Articles 8, 9 and 10 of the Stanford License Agreement, such that Stanford may directly enforce Articles 8, 9 and 10 of the Stanford License Agreement against Santaris, and (c) if Stanford terminates the Stanford License Agreement as it relates to Regulus (but not as it relates to this Agreement), Santaris will assume (and be directly liable to Stanford for) all Third Party License Pass-Through Costs and all Third Party and Founding Company-Originated Rights and Obligations due Stanford in connection with this Agreement.

Term	Unless earlier terminated pursuant to Santaris' termination rights below, the license agreement would continue in full force and effect until the date of expiration of all payment obligations by Santaris under such license agreement (the "Santaris Agreement Term").

Santaris termination rights	Santaris would have the right, at its sole discretion, exercisable at any time during the Santaris Agreement Term, to terminate the license agreement in its entirety, for any reason or for no reason at all, upon ninety (90) days written notice to Regulus.

Appendix 1

The [***] Patents are all Patent Rights related to the following:

[***]

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R §§ 200.80(b)4, AND 240.24b-2

Execution Copy

LEASE AGREEMENT

THIS LEASE is entered into on March 30, 2010 (the "***Effective Date***"), by and between **BMR-GAZELLE COURT LLC**, a Delaware limited liability company (the "***Landlord***"), and **ISIS PHARMACEUTICALS, INC.**, a Delaware corporation (the "***Tenant***"). Landlord and Tenant are sometimes hereinafter referred to collectively as the "***parties***."

RECITALS

WHEREAS, Landlord owns that certain real property located within the Carlsbad Oaks North Business Park in Carlsbad, California more particularly described in Exhibit 'A' attached hereto (the "***Land***");

WHEREAS, Landlord intends to construct an approximately 176,000 square foot office, research and development facility on the Land substantially consistent with the Approved Plans (the ***"Building"***) and pursuant to the terms and conditions of this Lease;

WHEREAS, Landlord desires to lease the Land, as so improved, to Tenant pursuant to the terms and conditions of this Lease; and

WHEREAS, Tenant desires to lease the Land and such improvements from Landlord.

AGREEMENT

NOW, THEREFORE, Landlord and Tenant, in consideration of the mutual promises contained herein and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, and intending to be legally bound, agree as follows:

ARTICLE 1

Description of Premises; Construction of Improvements

1.1 Lease of Premises. Effective as of the Term Commencement Date, Landlord hereby leases to Tenant and Tenant leases from Landlord, pursuant to the terms, conditions and uses herein set forth, (a) the Land, and (b) any and all improvements owned by Landlord and now or hereafter located on the Land, including but not limited to the Building (collectively, the "***Improvements***"). The Land and the Improvements are hereinafter collectively referred to as the "***Premises***."

1.2 Landlord's Construction Work.

1.2.1 Entitlements. Landlord shall diligently pursue the procurement of all permits, approvals, and entitlements necessary for the construction of Landlord's Construction Work on the Land (collectively, the "***Entitlements***").

1.2.2 Landlord's Construction Work. Promptly following the date on which the Entitlements necessary for the construction of the Shell and Core, or Tenant Improvements, as applicable, have been received and are no longer subject to any potential appeal or challenge and the Approved Plans exist, or on such earlier date as Landlord may elect in its discretion, Landlord shall cause the General Contractor to commence and diligently prosecute the construction of (i) the shell and core of the Building to completion pursuant to the Approved Shell and Core Plans (the ***"Shell and Core"***), and (ii) the tenant improvements in the Building pursuant to the Approved TI Plans (the "***Tenant Improvements***"), in each case in accordance with the terms and conditions set forth in the Work Letter attached hereto as Exhibit 'B' (the "***Work Letter***"), subject only to Shell and Core Permitted Changes, TI Permitted Changes and any other changes authorized pursuant to the Work Letter (all such construction, the "***Landlord's Construction Work***"); provided, Landlord will not be required to start the fine grading before the necessary Entitlements for the Shell and Core have been received and are no longer subject to any potential appeal or challenge. The Shell and Core, together with the Tenant Improvements shall collectively be referred to herein as the "***Building Improvements***". Landlord's Construction Work shall be constructed in a good and workmanlike manner, and in accordance with Applicable Laws (subject only to (a) such incomplete or defective work as will not materially adversely impact Tenant's continuous and uninterrupted use of the Premises for Tenant's Permitted Use (collectively, the "***Punchlist Items***") and (b) any failure to comply with Applicable Laws as will not materially adversely impact Tenant's continuous and uninterrupted use of the Premises for Tenant's Permitted Use).

1.2.3 Substantial Completion of Landlord's Construction Work. Landlord's Construction Work shall be deemed "***Substantially Complete***" or there shall be "***Substantial Completion***" at such time as (a) Landlord and Tenant have received an AIA form certificate from the Architect confirming that the Building Improvements are substantially complete in accordance with the Approved Plans, (b) all certifications and approvals with respect to the Building Improvements that may be required from any Governmental Authority to commence the occupancy of the Premises consistent with the Permitted Use have been obtained, and (c) Landlord has provided Tenant with continuous and uninterrupted access to the Premises for Tenant's Permitted Use (including Tenant's parking), except to the extent reasonably necessary for Landlord's General Contractor to complete the Punchlist Items. The date on which Landlord' Construction Work is deemed Substantially Complete pursuant to the foregoing shall be referred to herein as the "***Substantial Completion Date***."

1.2.4 Schedule and Budget. Landlord estimates that the Substantial Completion Date shall occur on or before November 15, 2011 (the ***"Estimated Substantial Completion Date"***); provided, however, except as expressly provided under Section 19.2 and Section 19.3.4, Tenant agrees that in the event the Substantial Completion Date does not occur on or before the Estimated Substantial Completion Date for any reason, then this Lease shall not be void or voidable and Landlord shall not be liable to Tenant for any loss or damage resulting therefrom. Based solely on information provided by the Project Manager, Landlord currently intends to complete construction of the Building Improvements in accordance with the Budget (as defined in the Work Letter); provided, the parties acknowledge and agree the actual cost and expense to complete construction of the Building Improvements may exceed the Budget. If Landlord reasonably believes the costs and expenses of achieving Substantial Completion of Landlord's Construction Work will exceed the contemplated

costs and expenses thereof as set forth in the Budget, then Landlord will promptly notify Tenant's Authorized Representative (by telephone, fax, email, or letter) thereof.

1.3 Construction Allowance. Subject to the terms and provisions of this Lease, Landlord hereby commits to expend the funds necessary to acquire the Land and develop and construct the Building Improvements (the "***Construction Allowance***"). The Construction Allowance shall be applied only to the costs and expenses of (a) Tenant's acquisition of the Land from Techbilt Construction Corp (***"Techbilt"***) and the acquisition of the Land by Landlord from Tenant, including all closing costs and expenses thereof, (b) reimbursements to Tenant for the costs specified on Exhibit I attached hereto (such reimbursement to be made on or before the Effective Date), (c) construction, (d) space planning, architectural services, project management, engineering and other related services, (e) building permits and other taxes, fees, charges and levies by any Governmental Authority for the Entitlements or for inspections of the Building Improvements, (f) labor, material, buildings, building systems, equipment, fixtures, machinery, additions and decorations (g) all Real Estate Taxes assessed or imposed for the period prior to the Term Commencement Date, (h) all Association Fees assessed or imposed for the period prior to the Term Commencement Date, (i) all utilities and other out-of-pocket operating costs necessary for development and construction, or for operation of the Premises prior to the Term Commencement Date, (j) Landlord's builder's risk insurance policy and any deductibles thereunder or deficiencies necessary to be paid in order to reconstruct the Building Improvements following any damage or destruction that occurs prior to the Term Commencement Date, (k) any other insurance obtained by Landlord pursuant to the terms of this Lease prior to the Term Commencement Date, (l) all other out-of-pocket costs of operating, maintaining and repairing the Premises before the Term Commencement Date; (m) proposing, responding to proposals for or effecting changes or modifications to any plans or designs for the Building Improvements; (n) the costs of performing the Baseline Study under Section 7.1.3; (o) amounts paid to the architects, engineers or contractors to compensate them for the actual cost to obtain access to or use of intellectual property (such as software), if any, that is necessary or desirable for the design or construction of the Building Improvements; and (p) any other costs and expenses necessary for the acquisition, development and construction of the Premises as determined by Landlord in its reasonable discretion (collectively, the "***Construction Allowance Costs***"). By way of example and for clarity purposes only, Landlord may disburse the Construction Allowance to pay for the expenses set forth in the line items specified in the Budget. In no event shall the Construction Allowance be used for (v) the costs set forth on Exhibit E attached hereto (except for the out-of-pocket legal expenses reasonably incurred in connection with Landlord's acquisition of the Land, the negotiation of the Lease or Landlord's Construction Work), (w) the cost of work not authorized by the Work Letter unless otherwise approved in writing by Landlord, (x) the purchase of non-building system equipment (other than any non-building system equipment specifically included in the Budget or installed by Landlord as part of the Landlord's Construction Work), (y) costs resulting from any default by Tenant of its obligations under this Lease, to the extent that Landlord has been reimbursed for such costs by Tenant, or (z) costs that are recoverable from a third party (e.g., insurers, warrantors, or tortfeasors). For purposes of this Lease, any Construction Allowance funds delivered by Landlord to pay any Construction Allowance Costs shall be deemed to constitute "***Disbursements***", and ***"Aggregate Disbursements"*** will mean (i) the aggregate amount of Construction Allowance funds disbursed by Landlord for the Construction Allowance Costs, plus (ii) capitalized interest calculated on each such Disbursement based on the aggregate amount of Construction Allowance funds disbursed (including, without limitation, any previously incurred capitalized interest) at the rate of LIBOR plus [***]% per annum, such interest to compound

monthly and to accrue starting on the last day of the month in which Landlord made such Disbursement and ending on the Substantial Completion Date. ***"LIBOR"*** means the London InterBank Offered Rate of interest per annum which appears on the Reuters Page LIBOR01 (or any successor page) at approximately 11:00 a.m. (London time) on the last day of the month in which Landlord made the applicable disbursement; provided, if, for any reason, such rate does not appear on Reuters Page LIBOR01 (or any successor page) then the parties will mutually agree in good faith to a comparable measure for setting the base interest rate. The procedures, conditions and requirements concerning the disbursement of Construction Allowance funds are set forth in the Work Letter.

ARTICLE 2

Term

2.1 Binding Agreement. This Lease shall take effect as of the Effective Date and, except as specifically provided herein, this Lease and each of the provisions hereof shall be binding upon, and shall inure to the benefit of, Landlord and Tenant from the Effective Date.

2.2 Lease Term. The term of this Lease will be for two hundred forty (240) months commencing on the Substantial Completion Date (the "***Term Commencement Date***") and ending on the date (the "***Term Expiration Date***") that is two hundred forty (240) months after the Term Commencement Date (the "***Lease Term***"), subject to earlier termination of this Lease as provided herein; provided, however, that Tenant shall have four (4) options to extend the Lease Term, as further described in Article 36. Tenant shall execute and deliver to Landlord written acknowledgment of the actual Term Commencement Date and the Term Expiration Date within ten (10) days after Tenant takes occupancy of the Premises, in the form attached as Exhibit 'H' hereto. Failure to execute and deliver such acknowledgment, however, shall not affect the Term Commencement Date or Landlord's or Tenant's liability hereunder.

ARTICLE 3

Rent

3.1 Base Monthly Rental.

3.1.1 Calculation of Base Monthly Rental. Beginning on January 1, 2012 (the "***Base Monthly Rent Commencement Date***"), Tenant shall pay to Landlord at the address set forth in Section 35.10, or such other address as Landlord may advise Tenant in writing, without deduction, offset or prior notice or demand, and Landlord shall accept, as rent for the Premises an amount equal to the Base Monthly Rental, subject to adjustments pursuant to Section 3.3 below, in lawful money of the United States payable in advance on the Base Monthly Rent Commencement Date and on the first day of each month thereafter until of the end of the Lease Term. The term "***Base Monthly Rental***" shall mean an amount equal to (i) the product of (a) [***] percent ([***]%) and (b) the sum of the Aggregate Disbursements disbursed as of the date of such calculation of Base Monthly Rental plus an amount equal to the Construction Allowance funds that will be allocable pursuant to the provisions of this Lease to the payment of all invoices or requests for payment relating to the Construction Allowance Costs which have

been received by Landlord or Tenant but which are not yet paid as of the date of such calculation of Base Monthly Rental (the "***Pending Disbursements***"); (ii) divided by twelve (12), subject to adjustments pursuant to Sections 3.2, 3.3 and 36.2 below. Except for as explicitly provided in Section 3.2.2, when calculating Base Monthly Rental, all Disbursements made by Landlord during a given month, including Disbursements made following the Base Monthly Rent Commencement Date, are treated to have occurred on the last calendar day of the month. From and after the Base Monthly Rent Commencement Date through the date the Building Improvements will be deemed Complete pursuant to Section 8 of the Work Letter (the "***Punchlist Sign-off Date***"), Tenant shall pay Base Monthly Rental as calculated pursuant to this Section 3.1.1, with true-ups as provided in Section 3.2.2.

3.1.2 Limit on Tenant's Maximum Payments During Construction. Notwithstanding any provision of this Lease (or any other agreement between Tenant and Landlord entered into in connection with this Lease) to the contrary, at any time prior to the Substantial Completion Date, the aggregate amount of all payments made or expenses incurred by Tenant under this Lease (or any other agreement between Tenant and Landlord entered into in connection with this Lease), including but not limited to (a) Base Monthly Rental paid by Tenant, and (b) Tenant's indemnification obligations pursuant to Section 4.3.3 hereof, shall not (and will not) exceed eighty-nine percent (89%) of the sum of the Aggregate Disbursements made by Landlord that are properly capitalizable under US GAAP at such point in time (the "***89% Cap***"); provided, however, that (i) if and to the extent that Tenant's payment obligations under this Lease or any agreement between Tenant and Landlord entered into in connection with this Lease are limited by the 89% Cap, so that Tenant does not make any payment to Landlord to which Landlord would have been entitled if not for the 89% Cap, then Tenant shall pay such amount (plus interest at the Default Rate) to Landlord within three (3) business days after the Term Commencement Date, and (ii) the 89% Cap shall not apply to (A) any obligations of Tenant pursuant to any representations, warranties or indemnities by Tenant contained in that certain Agreement of Purchase and Sale between Landlord and Tenant dated as of the date hereof, or (B) any obligations of Tenant pursuant to any representations, warranties or indemnities by, or monetary obligations of, Tenant arising under any Purchase and Sale Agreement entered into pursuant to Sections 19.1.4 or 24.2.

3.2 Determination of Base Monthly Rental.

3.2.1 Initial Rent. Promptly following December 15, 2011, the parties shall cooperate to agree upon the calculation of the Base Monthly Rental payment due on the Base Monthly Rent Commencement Date, with such calculation to be agreed upon in writing by the parties no later than December 23, 2011.

3.2.2 True-Up at Substantial Completion Date and Punchlist Sign-off Date. The parties contemplate that the Punchlist Sign-off Date will occur on or before December 15, 2011. If the Punchlist Sign-off Date has not occurred by December 15, 2011, then (a) the parties will initially calculate the Base Monthly Rental in accordance with Section 3.1.1 and 3.2.1, and (b) Tenant will initially pay Base Monthly Rental under this Lease based on such calculation (subject to further adjustment in accordance with (i) the 89% Cap, if the Base Monthly Rent Commencement Date occurs prior to the Substantial

Completion Date, and (ii) this Section 3.2.2). Promptly (but no later than 10 business days) following each of (x) the Substantial Completion Date, (y) the Punchlist Sign-off Date, and (z) the end of each calendar month between the Substantial Completion Date and the Punchlist Sign-off Date (if any), the parties will recalculate and adjust the Base Monthly Rental effective as of the date of such recalculation based on the Aggregate Disbursements through the date of recalculation and the then current Pending Disbursements as of such date, using the formula and methodology set forth in Section 3.1.1, and Tenant shall pay Base Monthly Rental based on the recalculated amount from and after the date of recalculation.

3.2.3 Unused Construction Allowance. Following the Punchlist Sign-off Date, Landlord shall have no commitment to disburse any additional Construction Allowance funds and Tenant shall have no right to receive any additional Construction Allowance funds for any purpose.

3.3 Biennial Adjustments. The Base Monthly Rental will be increased biennially throughout the Lease Term commencing on the first day of the calendar month immediately following the second anniversary of the Base Monthly Rent Commencement Date, and biennially on each two-year anniversary thereafter, by an amount equal to six percent (6%) of the Base Monthly Rental for the preceding year.

3.4 Additional Rent, Expenses and Costs. Commencing on the Term Commencement Date and continuing throughout the Lease Term, Tenant shall pay as additional rent (in addition to Base Monthly Rental), before delinquency, each and every item of cost and expense related to or arising from the Premises, or by reason of or in any manner connected with or arising from the Tenant's operation, management, maintenance, repair, use or occupancy of the Premises (including, without limitation, the cost of: insurance pursuant to Section 10, taxes pursuant to Section 12, maintenance, roof and structural repairs pursuant to Sections 11.1 and 11.2, and other charges, expenses and costs provided for in this Lease), in each case regardless of whether such costs and expenses are incurred by Landlord or Tenant (collectively, the "***Additional Rent***"). Notwithstanding anything to the contrary in this Lease, in no event will Additional Rent or any other expense to be paid by Tenant include the costs and expenses listed on Exhibit 'E' attached hereto. For purposes of this Lease, "***Rent***" will mean the Base Monthly Rental plus the Additional Rent plus any other charges or amounts now or hereafter due Landlord from Tenant pursuant to this Lease.

3.5 Late Fees. Tenant acknowledges that late payment by Tenant of the Base Monthly Rental, any Additional Rent, or other charges incurred under this Lease will cause Landlord to incur costs not contemplated by this Lease, the exact amount of such costs being extremely difficult and impracticable to fix. Such costs include, without limitation, processing, administrative and accounting charges. If any payment of Base Monthly Rental, Additional Rent, or other charges due from Tenant is not received by Landlord within five (5) business days of when due, such unpaid amounts shall bear interest at the rate of eight percent (8%) per annum ("***Default Rate***") from the date due to the date of payment. In addition to interest, Tenant shall pay a sum of the greater of (i) 3% of the overdue Rent or (ii) $15.00 as a late charge; provided, however, that twice but only twice in any twelve (12) month period from and after the Base Monthly Rent Commencement Date until the termination or expiration of the Lease Term, Tenant shall be entitled to written notice of non-receipt of Base Monthly Rental or Additional Rent from Landlord, and Tenant shall not be liable for any late charge hereunder with respect

thereto if such installment of Base Monthly Rental or Additional Rent is received by Landlord within five (5) days after Tenant's receipt of such notice from Landlord. Late charges shall constitute Additional Rent. The parties agree that the late charge represents a fair and reasonable estimate of the costs that Landlord will incur by reason of late payment by Tenant. Acceptance of any late charge shall not constitute a waiver of Tenant's default with respect to the overdue amount, or prevent Landlord from exercising any of the other rights and remedies available to Landlord hereunder.

3.6 Tenant's Audit Right.

3.6.1 Following the Punchlist Sign-off Date, but no later than one-hundred twenty (120) days after such Punchlist Sign-off Date, Tenant may request that Landlord provide documentation relating to the amount of Aggregate Disbursements made prior to such date. In addition, at the end of each calendar year during the Lease Term, but no later than one-hundred twenty (120) days after the end of such calendar year, Tenant may request that Landlord provide documentation relating to the costs and expenses that comprised the Additional Rent for such year. Landlord shall use commercially reasonable efforts to provide Tenant with the requested documentation; *provided*, *however*, that Landlord shall only be required to provide such documentation to the extent that the requested documentation (a) is reasonably necessary for Tenant to confirm that the Aggregate Disbursements tie back to the Construction Allowance Costs, or confirm the calculation of Additional Rent, (b) is in Landlord's possession, and (c) has not been previously provided to Tenant by Landlord or any other party (the ***"Landlord Documentation"***). Tenant shall have the right, exercisable only by written notice to Landlord within sixty (60) days after receiving the applicable Landlord Documentation, to request an audit of such Landlord Documentation for the sole purpose of confirming that the Aggregate Disbursements tie back to the Construction Allowance Costs, or the calculation of Additional Rent, as applicable (the ***"Audit"***). The Audit shall be conducted by a member of a reputable, independent, nationally recognized certified public accounting firm, who (a) has experience reviewing records of construction and development costs for similar projects (in the case of an Audit of the Aggregate Disbursements) or (b) who has experience reviewing operating costs and expenses for similar projects (in the case of an Audit of Additional Rent), and, in either case, such accountant shall not be retained by Tenant on a contingency fee basis. The Audit must be completed no later than ninety (90) days after Tenant receives the applicable Landlord Documentation, and any audit report prepared by Tenant's auditors shall be delivered concurrently to Landlord and Tenant within the ninety (90) day period, or Tenant shall be deemed to have waived its Audit right. Tenant shall pay all costs of the Audit. In addition, if as part of such Audit, Tenant requests Landlord prepare copies of the Landlord Documentation for review by Tenant or its auditors outside of Landlord's principal place of business (rather than or in addition to Landlord making the Landlord Documentation available for review at Landlord's principal place of business), then Tenant shall reimburse Landlord for the reasonable costs of assembling and/or shipping such copies of the Landlord Documentation.

3.6.2 If, after inspection of the Landlord Documentation, Tenant disputes that the Aggregate Disbursements tie back to the Construction Allowance Costs, or the calculation of Additional Rent, then Landlord and Tenant shall meet and attempt in good faith to resolve the dispute. If the parties are unable to resolve the dispute within sixty (60) days after Landlord receives such audit report, then Tenant shall have the right to submit the dispute to

arbitration; this right shall be exercised, if at all, by delivering a written notice of election to arbitrate to Landlord not later than the last day of the 60-day period. Landlord and Tenant shall agree, within fifteen (15) days after Tenant's delivery of the arbitration election, to retain an arbitrator who shall be an unaffiliated real estate attorney with at least ten (10) years of experience representing developers of similar projects in Southern California. If Landlord and Tenant are unable to agree upon the selection of an arbitrator, then either Landlord or Tenant shall be entitled to apply to the presiding judge of the Superior Court of the County of San Diego, California for the selection of an arbitrator who shall be selected from a list of names of experienced arbitrators submitted by Landlord or from a list of names submitted by Tenant, as the case may be, unless both Landlord and Tenant submit lists of names, in which case the Court, in its sole discretion, shall select the arbitrator from the lists. This arbitrator shall have the right to retain, as an expert to consult regarding the dispute, an unaffiliated, reputable certified public accountant who is a member of a reputable independent nationally recognized certified public accounting firm and (a) who has experience reviewing records of construction and development costs for similar projects (in the case of an Audit of the Aggregate Disbursements) or (b) who has experience reviewing operating costs and expenses for similar projects (in the case of an Audit of Additional Rent). The arbitration shall be limited to determining whether the Aggregate Disbursements tie back to the Construction Allowance Costs, or the calculation of Additional Rent, as applicable. The arbitrator's decision shall be delivered simultaneously to Landlord and Tenant and shall be final and binding on Landlord and Tenant.

3.6.3 If the arbitrator determines that the amount of Aggregate Disbursements or Additional Rent, as applicable, was incorrect, the appropriate party shall pay to the other party the deficiency or overpayment in Rent, as applicable, within thirty (30) days following delivery of the arbitrator's decision, without interest. All costs and expenses of the arbitration shall be paid by Tenant unless the final determination in the arbitration is that Landlord overstated Aggregate Disbursements or Additional Rent, as applicable, by more than five percent (5%) of the originally reported Aggregate Disbursements or Additional Rent, as applicable, in which case Landlord shall pay all costs and expenses of the arbitration (and the costs and expenses of Tenant's audit giving rise to such arbitration).

3.6.4 Tenant shall keep any information gained from the inspection of the Landlord Documentation confidential and shall not disclose it to any other party, except as required by law. Tenant shall require its employees or agents inspecting the Landlord Documentation to sign a confidentiality agreement, in form and substance reasonably acceptable to Landlord as a condition to Landlord making the Landlord Documentation available to them.

3.6.5 Tenant's exercise of Audit rights shall not relieve Tenant of the obligation to pay disputed amounts, and Tenant's rights under this section may be exercised by Tenant only if Tenant is not in uncured breach under this Lease. The payment by Tenant of Rent, or any amount of it on account, shall not preclude Tenant from exercising its rights under this section, but if Tenant fails to timely exercise its Audit rights in accordance with this section, the failure shall be conclusively deemed to constitute Tenant's approval of Landlord's Aggregate Disbursements or Additional Rent, as applicable. Landlord shall maintain the Landlord Documentation pertaining to Aggregate Disbursements and Additional Rent, as applicable, during the review period and during any Audit. In no event shall this section be deemed to allow any review of any of Landlord's records by any subtenant or assignee of Tenant (other than assignees under Exempt Assignment as permitted by Section 16.3).

3.7 Security Deposit.

3.7.1 Tenant shall not be required to post any security deposit with the Landlord prior to the Term Commencement Date. In addition, during the Lease Term Tenant shall not initially be required to post any security deposit with the Landlord; provided, however, that in the event that, at any time during the Lease Term, Tenant's balance sheet reflects a value of cash, cash equivalents and short term investments equal to less than One Hundred

Million Dollars ($100,000,000) (each such occurrence, a "***Security Deposit Trigger Event***"), then Tenant shall be required to provide Landlord with a security deposit (the "***Security Deposit***") in the form of an unconditional, irrevocable, standby letter of credit in the amount of Five Million Dollars ($5,000,000), which letter of credit shall (i) be in a form reasonably acceptable to Landlord, (ii) be issued by a financial institution selected by Tenant and reasonably acceptable to Landlord, (iii) be for the benefit of Landlord, but shall be transferable at Tenant's sole cost and expense by Landlord to any subsequent purchaser or encumbrancer of the Premises or any portion thereof, (iv) be automatically renewable from year to year throughout the Lease Term, (v) be payable by draft sight in a location reasonably acceptable to Landlord upon presentation of a certification signed by an officer of Landlord which states that Tenant has failed to perform any of its monetary or non-monetary obligations, and (vi) be payable in the event such letter of credit is not renewed on or before the date which is thirty (30) days prior to its expiration. Such Security Deposit shall remain in place until Tenant provides Landlord with evidence satisfactory to Landlord that Tenant's balance sheet reflects a value of cash, cash equivalents and short term investments equal to or greater than Three Hundred Million Dollars ($300,000,000); provided, however, that any such return of the Security Deposit shall not relieve Tenant of its obligation to thereafter again provide a Security Deposit following any subsequent Security Deposit Triggering Event(s). For purposes of clarity, if a Security Deposit Trigger Event occurs prior to the Term Commencement Date, Tenant will provide the Security Deposit to Landlord on (but not before) the Term Commencement Date.

3.7.2 If Tenant fails to pay Rent when required or fails to perform any other covenant contained herein, Landlord may draw, use or retain all or any part of the Security Deposit for the payment of any sum not so paid, or for the payment of any amount which Landlord may spend or become obligated to spend by reason of Tenant's default. If any portion of said Security Deposit is so applied or used, then Tenant shall, within five (5) days after written notice thereof, deposit an additional amount with Landlord sufficient to restore said Security Deposit to the amount set forth above, and Tenant's failure to do so shall constitute a breach under this Lease. The provisions of this Section 3.6.2 shall survive the expiration or earlier termination of this Lease.

3.7.3 To the extent permitted by Applicable Law, in the event of bankruptcy or other debtor-creditor proceedings against Tenant, the Security Deposit shall be deemed to be applied first to the payment of Rent and other charges due Landlord for all periods prior to the filing of such proceedings.

3.7.4 If Tenant has performed all of its monetary and other obligations hereunder at the termination of this Lease, Landlord shall return said Security Deposit to Tenant within 30 days after termination of this Lease, less the sum of any amounts that Tenant may owe Landlord in connection with this Lease (including any amount of damages (whether liquidated or not liquidated) or interest) and any amounts required to restore the Premises to good condition and repair, reasonable wear and tear excepted, including repairing any damage resulting from the removal by Tenant of any property which Tenant is permitted to remove pursuant to the provisions of this Lease.

3.7.5 Landlord's obligation with respect to any Security Deposit is that of a debtor and not as a trustee. Consequently, any Security Deposit funds may be commingled with rental receipts or dissipated and no interest shall accrue thereon.

3.7.6 In the event of the sale of the Premises, Landlord's successor in interest shall assume Landlord's obligations with respect to the sums held as security and notify Tenant in writing setting forth the particularity of such transfer, including the successor's name and address. Upon such assumption and written notification, Tenant shall have no further claim against Landlord with respect to any such Security Deposit and hereby waives all rights against Landlord in such regard. Notwithstanding the foregoing, Landlord will remain personally liable to the extent Landlord's successor in interest fails to assume the Landlord's obligations with respect to the Security Deposit as specified above.

3.7.7 In the event of foreclosure by the holder of any mortgage or deed of trust encumbering the Premises, Landlord shall continue to be liable for any security deposit and any such mortgagee shall have no liability or responsibility therefore, except to the extent the Security Deposit is delivered to such mortgagee and such mortgagee assumes responsibility for such Security Deposit.

ARTICLE 4

Possession

4.1 Possession. As of the Substantial Completion Date, Landlord shall tender possession of the Premises to Tenant. Tenant hereby acknowledges and agrees that (a) it is familiar with the condition of the Premises, (b) it, subject to Punchlist Items, accepts the Premises as of the Substantial Completion Date in its "as is" and "where is" condition with all faults, (c) Landlord makes no representation or warranty of any kind with respect to the Premises, and (d) other than constructing the Building Improvements and the Punchlist Items in accordance with this Lease and as explicitly required under Article 20 and 21, Landlord will have no obligation whatsoever to improve, alter or repair the Premises in any way, or to install any equipment of any kind in or on the Premises.

4.2 NOTWITHSTANDING ANYTHING TO THE CONTRARY HEREIN, IT IS EXPRESSLY UNDERSTOOD AND AGREED THAT LANDLORD IS LEASING THE PREMISES TO TENANT "AS IS" AND "WHERE IS," AND WITH ALL FAULTS (EXCEPT FOR LANDLORD'S OBLIGATION TO COMPLETE THE PUNCHLIST ITEMS), AND THAT LANDLORD IS MAKING NO REPRESENTATIONS OR WARRANTIES WHETHER

EXPRESS OR IMPLIED, BY OPERATION OF LAW OR OTHERWISE, WITH RESPECT TO THE QUALITY OR PHYSICAL CONDITION OF THE PREMISES, THE INCOME OR EXPENSES FROM OR OF THE PREMISES, OR THE COMPLIANCE OF THE PREMISES WITH APPLICABLE BUILDING OR FIRE CODES, ENVIRONMENTAL LAWS OR OTHER LAWS, RULES, ORDERS OR REGULATIONS. WITHOUT LIMITING THE FOREGOING, IT IS UNDERSTOOD AND AGREED THAT LANDLORD MAKES NO REPRESENTATION OR WARRANTY REGARDING THE HABITABILITY, SUITABILITY, MERCHANTABILITY OR FITNESS OF THE PREMISES FOR A PARTICULAR PURPOSE, OR REGARDING THE ABILITY OF THE TENANT TO USE THE BUILDING IMPROVEMENTS OR OTHERWISE USE THE PREMISES FOR ANY PARTICULAR PURPOSE. TENANT AGREES THAT IT ASSUMES FULL RESPONSIBILITY FOR, AND THAT IT HAS PERFORMED EXAMINATIONS AND INVESTIGATIONS OF, THE PREMISES, INCLUDING SPECIFICALLY, WITHOUT LIMITATION, EXAMINATIONS AND INVESTIGATIONS FOR

THE PRESENCE OF ASBESTOS, PCBS AND OTHER HAZARDOUS SUBSTANCES, MATERIALS AND WASTES (AS THOSE TERMS MAY BE DEFINED HEREIN OR BY APPLICABLE FEDERAL OR STATE LAWS, RULES OR REGULATIONS) ON OR IN THE PREMISES.

4.2.1 WITHOUT LIMITING SECTION 4.2, TENANT IRREVOCABLY WAIVES ANY AND ALL CLAIMS AGAINST LANDLORD, WHETHER KNOWN OR UNKNOWN, AND WHETHER NOW EXISTING OR HEREAFTER ARISING, WITH RESPECT TO (a) THE MATTERS EXPLICITLY SET FORTH IN SECTION 4.2, AND (b) THE CURRENT OR FUTURE CONDITION OF THE PREMISES, INCLUDING, WITHOUT LIMITATION, ANY ENVIRONMENTAL CONDITION, IN EACH CASE INCLUDING CONTRIBUTION AND INDEMNITY CLAIMS, WHETHER STATUTORY OR OTHERWISE; PROVIDED, HOWEVER, THAT THE WAIVER OF CLAIMS SET FORTH IN THIS SECTION 4.2.1 SHALL NOT APPLY TO THE EXTENT THAT THE APPLICABLE CLAIM ARISES OUT OF (i) THE GROSS NEGLIGENCE OR WILLFUL MISCONDUCT OF LANDLORD OR LANDLORD'S AGENTS; OR (ii) LANDLORD'S BREACH OF THIS LEASE.

THE UNDERSIGNED ACKNOWLEDGES THAT IT HAS BEEN ADVISED BY LEGAL COUNSEL AND IS FAMILIAR WITH THE PROVISIONS OF CALIFORNIA CIVIL CODE SECTION 1542, WHICH PROVIDES AS FOLLOWS:

> "A GENERAL RELEASE DOES NOT EXTEND TO CLAIMS WHICH THE CREDITOR DOES NOT KNOW OR SUSPECT TO EXIST IN HIS OR HER FAVOR AT THE TIME OF EXECUTING THE RELEASE, WHICH IF KNOWN BY HIM OR HER MUST HAVE MATERIALLY AFFECTED HIS OR HER SETTLEMENT WITH THE DEBTOR."

THE UNDERSIGNED, BEING AWARE OF THIS CODE SECTION, HEREBY EXPRESSLY WAIVES ANY RIGHTS IT MAY HAVE THEREUNDER, AS WELL AS UNDER ANY OTHER STATUTES OR COMMON LAW PRINCIPALS OF SIMILAR EFFECT.

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Tenant's Initials

4.3 Tenant's Access and Obligations Prior to the Substantial Completion Date.

4.3.1 Upon reasonable prior written notice to Landlord, and so long as Tenant and Tenant's Agents do not (in Landlord's reasonable judgment) unreasonably or unnecessarily interfere with Landlord's Construction Work, Tenant may enter upon the Premises prior to the Term Commencement Date (any such entry to be deemed an "***Early Entry Event***") solely for the purpose of observing the progress of construction of the Building Improvements. Tenant shall not cause, and shall prevent Tenant's Agents from causing, any violation of Applicable Law through any act or omission in connection with an Early Entry Event.

4.3.2 Prior to the first Early Entry Event, Tenant shall furnish to Landlord evidence satisfactory to Landlord that Tenant has comprehensive general liability insurance in the amounts set forth in this Section 4.3.2, and that such insurance is in effect. Tenant hereby agrees that it shall comply and cause Tenant's Agents to comply with all Applicable Laws in effect at the time of any Early Entry Event.

4.3.2.1 From and after the first Early Entry Event, Tenant shall maintain in force, at its sole cost and expense, comprehensive general liability insurance with respect to the Premises insuring against bodily injury or death and property damage in amounts (i) not less than $2,000,000 in the aggregate, (ii) not less than $1,000,000 per occurrence and (iii) not less than $4,000,000 of excess umbrella liability insurance. Landlord shall be included as an additional insured. The amount of such public liability insurance shall be increased from time to time as Landlord may reasonably determine. All such bodily injury and property damage insurance shall insure the performance by Tenant of the indemnity agreement as to personal injury or property damage contained in Section 4.3.3

4.3.2.2 The policy or policies of insurance to be provided by Tenant pursuant to this Section 4.3.2 shall be issued by insurance companies, with general policy holder's rating of not less than A- and a financial rating of not less than Class VII as rated in the most current available "Best's" Insurance Reports, and admitted to do business in the State of California. Such policies shall be issued in the name of Tenant, with Landlord included as an additional insured. The policies provided by Tenant shall be for the mutual and joint benefit and protection of Landlord and Tenant, and executed copies of such policies of insurance or certificates thereof shall be delivered to the Landlord at least ten (10) days prior to the first Early Entry Event and, thereafter, within thirty (30) days prior to the expiration of the term of each such policy. All policies shall contain a provision that the Landlord, although an additional insured, shall nevertheless be entitled to recover under said policies for any loss occasioned to it or Landlord's Agents by reason of the negligence of the Tenant. Upon the expiration or termination of any such policy, renewal or additional policies shall be procured and maintained by the Tenant to provide the required coverage. All policies of insurance delivered to Landlord must contain a provision that the company writing said policy will provide Landlord with thirty (30) days notice in writing in advance of any cancellation or lapse or the effective date of any reduction in the amounts of insurance (except in the event of non-payment of premium, in which case ten (10) days written notice shall be given). All public liability, property damage and other casualty policies shall be written as primary policies, not contributing with and not in excess of coverage which Landlord may carry. Tenant agrees that if Tenant does not take out and maintain the insurance required under this Section 4.3.2, then Tenant shall lose any right to access the Premises pursuant to this Lease prior to the Term Commencement Date.

4.3.2.3 Notwithstanding any provision of this Lease to the contrary, Tenant's obligation to carry the insurance described in this Section may be brought within the coverage of a so-called blanket policy or policies of insurance carried and maintained by the Tenant, provided that (i) Landlord will be an additional insured thereunder as its interests may appear, (ii) the coverage afforded Landlord will not be reduced or diminished by reason of the use of such blanket policy of insurance, and (iii) the requirements set forth herein are otherwise satisfied. Tenant agrees to permit Landlord at all reasonable times to inspect the policies of insurance of Tenant covering the Premises for policies which are not required to be delivered to Landlord.

4.3.3 Tenant hereby agrees to indemnify, defend (with attorneys approved by Landlord), protect, and hold Landlord and Landlord's employees, directors and officers harmless from, any and all demands, claims, liabilities, costs, expenses, suits, investigations, proceedings, losses, actions, causes of action, damages and judgments (and all reasonable expenses including, without limitation, reasonable attorneys' fees, charges and disbursements incurred in investigating or resisting the same) (collectively, "***Claims***") to the extent (a) relating to acts, omissions or circumstances arising from an Early

Entry Event, and (b) caused by or arising out of (i) the acts or omissions of Tenant, its employees, agents, directors, officers, managers, members, partners, affiliates, independent contractors, consultants, property managers or invitees (collectively, "***Tenant's Agents***"), including without limitation, any liability for injury to the person or property of Tenant or Tenant's Agents, or (ii) a breach or default by Tenant in the performance of any of its obligations under this Lease; but in each case excepting any such Claims to the extent resulting from the willful breach of the Lease by Landlord or the gross negligence or willful misconduct of Landlord. Notwithstanding the foregoing, Tenant's obligations under this Section 4.3.3 shall be governed by the provisions set forth in Sections 9.4 and 9.5 hereof and are subject to the 89% Cap under Section 3.1.2 hereof. Tenant's obligations under this Section 4.3.3 shall survive the expiration or earlier termination of this Lease with respect to any such Claims or liability arising in connection with any event, condition or circumstance occurring, arising or existing prior to such expiration or earlier termination.

ARTICLE 5

Use

5.1 Permitted Use of Premises. The Premises shall be used and occupied by Tenant solely for office, research and development purposes in conformity with Applicable Laws and the provisions of this Lease (the "***Permitted Use***"). The Premises are to be used for no other purposes without first obtaining the consent of Landlord, which consent shall not be unreasonably withheld.

5.2 Compliance with Laws. Following the Term Commencement Date, Tenant, at Tenant's sole expense, shall promptly comply, or cause compliance, with all federal, state, municipal and local laws, codes, ordinances, zoning restrictions, rules, regulations, orders and

requirements of any federal, state, regional, local or municipal governmental authority, agency or subdivision (each, a "***Governmental Authority***"), committees, associations or other regulatory committees, agencies or governing bodies having jurisdiction over the Premises, Landlord or Tenant, in each case to the extent now or hereafter affecting the Premises (collectively, the "***Applicable Laws***"), including both statutory and common law and hazardous waste rules and regulations. Tenant shall not use or occupy the Premises in violation of Applicable Laws, or the certificate of occupancy issued for the Building Improvements, and shall, upon five (5) days' written notice from Landlord, discontinue any use of the Premises that is declared or claimed by any Governmental Authority having jurisdiction to be a violation of any of the above, or that in Landlord's reasonable opinion (based upon advice from Landlord's counsel) violates any of the above. Tenant shall comply with any direction of any Governmental Authority having jurisdiction that shall, by reason of the nature of Tenant's use or occupancy of the Premises, impose any duty upon Tenant or Landlord with respect to the Premises or with respect to the use or occupation thereof. Tenant's obligation to discontinue a use of the Premises or comply with any direction of any Governmental Authority will be stayed during the pendency of any dispute or request for a waiver or variance made in good faith by Tenant and submitted to such Governmental Authority, but in each case only so long as (a) any such non-compliance (alleged or actual), dispute or request for waiver could not reasonably be construed to constitute a criminal act by Landlord or Tenant or subject Landlord to a risk of any fine or penalty, (b) any such non-compliance (alleged or actual), dispute or request for waiver creates no risk of a lien, charge, or other liability of any kind against the Premises (unless Tenant shall have provided Landlord with reasonable security therefor), and (c) any such non-compliance (alleged or actual), dispute or request for waiver will not place the Premises or any portion thereof in any danger of being materially damaged, forfeited or lost and does not pose any danger to human health or safety. Notwithstanding anything to the contrary in this Lease, should Landlord's Construction Work fail to comply with Applicable Laws under clause (b) of Section 1.2.2, such failure to comply with Applicable Laws will not be considered a violation by Tenant of its obligations under this Section 5.2.

5.3 Prohibited Uses. Without limiting the use restrictions specified in Article 5 or elsewhere in this Lease, Tenant shall not do, bring or keep anything in or about the Premises that will cause a cancellation of any insurance covering the Premises or any portion thereof. Tenant shall not use the Premises in any manner that will constitute waste, nuisance or unreasonable annoyance to owners or occupants of nearby properties. Tenant shall not do anything on the Premises that will cause material damage to the Premises or any portion thereof. Tenant shall place no loads upon the floors, walls or ceiling of any Building Improvements (a) in excess of the maximum designed load specified in the design plans for the Premises as approved and permitted by the City of Carlsbad (and which design plans must also comply with the provisions of this Lease), or (b) which may materially damage the Improvements. No machinery, apparatus, or other appliance shall be used or operated in or on the Premises that will vibrate or shake the Premises.

5.4 Rules and Regulations. Tenant shall comply with all reasonable nondiscriminatory rules and regulations (the "***Rules and Regulations***") from time to time adopted by Landlord with respect to the Premises. Notwithstanding anything to the contrary contained in this Lease, if any rule or regulation is in conflict with any term, covenant or condition of this Lease, this Lease shall prevail. In addition, no such rule or regulation, or any

subsequent amendment thereto adopted by Landlord, shall materially alter, reduce or adversely affect any of Tenant's rights or materially enlarge Tenant's obligations under this Lease. This Lease is subject to any recorded covenants, conditions or restrictions on the Premises or any portion thereof (the "***CC&Rs***"), including (without limitation) the Declaration of Covenants, Conditions and Restrictions for the Carlsbad Oaks North Business Park, recorded February 5, 2007 as Instrument No. 2007-0081082 in the Official Records of San Diego County, as the same may be amended, amended and restated, supplemented or otherwise modified from time to time; provided that any such amendments, restatements, supplements or modifications do not materially modify Tenant's rights or obligations hereunder. During the Lease Term, Tenant shall comply with the CC&Rs and shall pay any and all costs associated with such compliance (including, without limitation, any assessments or association dues) either directly or as Additional Rent.

ARTICLE 6

Alterations and Additions

6.1 Prohibited Alterations. Prior to the Term Commencement Date, Tenant shall not make any alterations, improvements or additions to the Premises. Following the Term Commencement Date, Tenant shall not make any alterations, improvements or additions to the Premises, except for non-structural alterations which do not impair the value of the Premises, and which do not exceed $1,000,000 per occurrence or an aggregate amount of $2,500,000 in any 12-month period, without obtaining Landlord's prior written consent, which consent shall not unreasonably be withheld, conditioned or delayed. Notwithstanding the foregoing, Tenant shall not make any alterations that affect the structural elements of the Premises or require a construction or building permit without Landlord's prior written consent, which consent may be granted or withheld in Landlord's sole and absolute discretion. Any such

improvements shall become part of the realty constituting the Premises and shall belong to Landlord, except to the extent specifically provided otherwise in Article 13. Tenant shall cause all alterations and improvements to be properly permitted and installed at Tenant's sole cost, by a licensed contractor, in a good and workmanlike manner, and in conformity with Applicable Laws. Each such licensed contractor and any subcontractor that performs work with a cost greater than $500,000, shall be subject to Landlord's approval, which approval shall not be unreasonably withheld, conditioned or delayed. Any such alterations that Tenant shall desire to make and which require the consent of Landlord shall be presented to Landlord in written form with detailed plans. Tenant shall: (i) acquire all applicable governmental permits, (ii) furnish Landlord with copies of both the permits and the plans and specifications before the commencement of the work, and (iii) comply with all conditions of said permits in a prompt and expeditious manner. Any alterations shall be performed in a workmanlike manner with good and sufficient materials, and in accordance with Landlord approved plans and specifications. Tenant shall, promptly upon completion of such alterations, furnish Landlord with as-built plans and specifications. During the course of construction of, and following completion of, any such alterations, improvements or additions to the Premises, Tenant shall provide to Landlord conditional and unconditional lien waivers (as appropriate, but in any event, including at least monthly during the course of construction unconditional waivers upon progress payments dated no sooner than the first day of the immediately preceding month from each contractor, and each subcontractor of any tier that (a) has performed any work, provided any supplies, materials or

equipment or provided a preliminary notice and (b) has not provided an unconditional waiver upon final payment) in California statutory form from all parties providing work, services or materials with regard to the same. For purposes of clarification, this Section 6.1 does not apply to the original construction of the Building Improvements.

6.2 Notice of Commencement. At least twenty (20) days prior to commencing any work relating to any alterations, improvements or additions to the Premises (the "***Tenant Alterations***"), Tenant shall notify Landlord in writing of the nature of such Tenant Alterations and the expected date of commencement of such work. Landlord shall have the right (but not the obligation) at any time thereafter to post and maintain on the Premises such notices as Landlord reasonably deems necessary to protect Landlord and the Premises from mechanics' liens, materialmen's liens or any other liens, including the posting of any notice of non-responsibility in accordance with California law. Tenant shall not commence any such work prior to the date which is twenty (20) days following Landlord's receipt of such notice from Tenant, unless otherwise agreed by Landlord. Tenant shall pay, when due, all claims for labor or materials furnished to or for Tenant for use in improving the Premises. Tenant shall not permit any mechanics' or materialmen's liens to be levied against the Premises arising out of work performed, materials furnished, or obligations to have been performed on the Premises by or at the request of Tenant. Tenant hereby indemnifies and holds Landlord harmless against loss, damage, attorneys' fees and all other expenses on account of claims of lien of laborers or materialmen or others for work performed or materials or supplies furnished for Tenant or its contractors, agents or employees. Tenant will remove or bond any lien(s) filed against the Premises in connection with any work performed or materials or supplies furnished, or any work, materials or supplies claimed to have been performed or furnished by or at the direction of (or for the benefit of) Tenant within ten (10) days from the date of the filing of the lien(s). In addition to any other remedies available to Landlord under this Lease, Landlord may remove such lien(s) at Tenant's expense and Tenant shall reimburse Landlord for all costs incurred by Landlord in connection with the removal of the lien(s), which amount shall be deemed Additional Rent, and shall include, without limitation, all sums disbursed, incurred or deposited by Landlord, including Landlord's costs, expenses and actual attorneys' fees, with interest thereon, at the Default Rate from the date of expenditure.

ARTICLE 7

Surrender of Premises

7.1 Conditions upon Surrender Upon the expiration or earlier termination of this Lease, Tenant shall surrender the Premises to Landlord in as good a condition as the Premises was in as of the Substantial Completion Date, normal wear and tear, casualty, condemnation and acts of God excepted, with all interior walls in good repair and repainted if marked, all carpets shampooed and cleaned, the HVAC equipment, plumbing, electrical and other mechanical installations in good operating order, and all floors cleaned and waxed, all to the reasonable satisfaction of Landlord. Tenant shall remove from the Premises all Tenant Alterations which Landlord requires Tenant to remove and all Tenant's personal property which Tenant is authorized to remove pursuant to this Lease, and shall repair any damage and perform any restoration work caused by such removal. If Tenant fails to remove such Tenant Alterations and Tenant's personal property which Tenant is authorized and obligated to remove pursuant to the

above, and such failure continues after the termination of the Lease, Landlord may, at its option, (a) retain such property and all rights of Tenant with respect to it shall cease, (b) place all or any portion of such property in public storage for Tenant's account without liability to Tenant for loss thereof or damage thereto, or (c) upon at least thirty (30) days written notice to Tenant, sell such property or any portion thereof at private sale and without legal process for such price as Landlord may obtain, and first apply the proceeds of such sale against any amounts due or to become due from Tenant to Landlord under this Lease and any actual and documented expenses incident to the removal, storage and sale of said personal property, and within thirty (30) days thereafter Landlord will remit any remaining proceeds to Tenant. Tenant shall pay to Landlord upon demand costs of removal of such Tenant Alterations and Tenant's personal property and storage and transportation costs of same, and the cost of repairing and restoring the Premises, together with attorneys' fees and interest at the Default Rate on said amounts, from the date of expenditure by Landlord. If the Premises are not so surrendered at the termination of this Lease, Landlord may, in its sole discretion, either (i) upon written notice to Tenant, treat Tenant as a month-to-month tenant at will, subject to all the terms, covenants and conditions of this Lease, or (ii) proceed with an unlawful detainer action and pursue all other rights and remedies available to Landlord.

7.1.1 No surrender of possession of any part of the Premises shall release Tenant from any of its obligations hereunder.

7.1.2 The voluntary or other surrender of this Lease by Tenant shall not effect a merger with Landlord's fee title or leasehold interest in the Premises or any portion thereof, unless Landlord consents in writing, and shall, at Landlord's option, operate as an assignment to Landlord of any or all subleases which may exist at such time.

7.1.3 At least ten (10) days prior to Tenant's surrender of possession of any part of the Premises, Tenant shall provide Landlord with (a) a facility decommissioning and hazardous materials closure plan for the Premises ("***Exit Survey***"), and (b) written evidence of all appropriate governmental releases obtained by Tenant in accordance with Applicable Laws, including, without limitation, laws pertaining to the surrender of the Premises and (c) a Phase I Environmental Assessment. In addition, Tenant agrees to remain responsible after the surrender of the Premises for the remediation of any

recognized environmental conditions set forth in the Exit Survey or Phase I Environmental Assessment and compliance with any recommendations set forth in the Exit Survey and Phase I Environmental Assessment, to the extent such conditions or recommendations did not exist in the Baseline Study (as defined below). Tenant's obligations under this Section 7.1.3 shall survive the expiration or earlier termination of the Lease. Prior to the Term Commencement Date, Landlord will obtain an Exit Survey and a Phase I Environmental Assessment (collectively, the ***"Baseline Study"***), and will provide Tenant a copy of such Baseline Study.

ARTICLE 8

Utilities

8.1 Utilities. Following the Term Commencement Date, Tenant shall make all arrangements for and pay for all water, sewer, gas, heat, light, power, telephone service and any other service or utility required at the Premises. Landlord shall not be liable for, nor shall any eviction of Tenant result from, any failure or interruption of any utility service being furnished to the Premises, and no such failure or interruption shall entitle Tenant to terminate this Lease, or receive any abatement or reduction of Rent, or relief from the operation of any covenant, obligation or agreement set forth in this Lease; provided, however, that Tenant will be entitled to Rent abatement in connection with any such failure or interruption to the extent Landlord receives lost rental income insurance proceeds with respect hereto.

ARTICLE 9

Indemnification

9.1 Indemnity of Landlord.

9.1.1 From and after the Term Commencement Date, Tenant hereby agrees to indemnify, defend (with attorneys approved by Landlord), protect, and hold Landlord and Landlord's agents, employees, directors, officers, managers, members, partners and affiliates (collectively, "***Landlord's Agents***") harmless from, any and all Claims arising after the Term Commencement Date to the extent caused by, arising out of, or related to, (a) the condition of the Premises or the use or occupancy of the Premises by Tenant and/or Tenant's Agents, or any other person or entity, including without limitation, any liability for injury to the person or property of Tenant or Tenant's Agents, (b) a breach or default by Tenant in the performance of any of its obligations under this Lease; but in each case *excepting* any such Claims (i) to the extent resulting from the willful breach of the Lease by Landlord or the gross negligence or willful misconduct of Landlord or Landlord's Agents or (ii) arising solely out of the condition of the Premises that Tenant demonstrates existed prior to the Term Commencement Date, except to the extent that such condition was caused by Tenant or Tenant's Agents. Tenant's obligations under this Section 9.1.2 shall survive the expiration or earlier termination of this Lease with respect to any such Claims or liability arising in connection with any event, condition or circumstance occurring, arising or existing prior to such expiration or earlier termination.

9.2 Waiver of Claims.

9.2.1 Tenant, as a material part of the consideration rendered to Landlord in entering into this Lease, hereby waives all existing and future Claims against Landlord and Landlord's Agents, whether known or unknown, for damages to goods, wares, machinery, trade fixtures, personal property, scientific research, records or other property of Tenant, Tenant's Agents or any other person, in each case located in or about the Premises, whether such damage or injury is caused by or results from the negligence of Landlord or Landlord's Agents, fire, steam, electricity, gas, water or rain, or from the breakage, leakage, obstruction or other defects of pipes, fire sprinklers, wires, appliances, plumbing, HVAC or lighting fixtures, or from any other cause, whether the said injury or damage results from conditions arising upon the Premises or any portion thereof, or from other sources or places, including any claims resulting from the actual or passive negligence of Landlord or Landlord's Agents, but excepting any claims resulting from the gross negligence or willful misconduct of Landlord or Landlord's Agents or breach of this Lease by Landlord. Notwithstanding the negligence of Landlord or Landlord's Agents, or breach of this Lease by Landlord, Landlord shall under no circumstances be liable for loss of profits or special, incidental or consequential damages arising therefrom.

THE UNDERSIGNED ACKNOWLEDGES THAT IT HAS BEEN ADVISED BY LEGAL COUNSEL AND IS FAMILIAR WITH THE PROVISIONS OF CALIFORNIA CIVIL CODE SECTION 1542, WHICH PROVIDES AS FOLLOWS:

> "A GENERAL RELEASE DOES NOT EXTEND TO CLAIMS WHICH THE CREDITOR DOES NOT KNOW OR SUSPECT TO EXIST IN HIS OR HER FAVOR AT THE TIME OF EXECUTING THE RELEASE, WHICH IF KNOWN BY HIM OR HER MUST HAVE MATERIALLY AFFECTED HIS OR HER SETTLEMENT WITH THE DEBTOR."

THE UNDERSIGNED, BEING AWARE OF THIS CODE SECTION, HEREBY EXPRESSLY WAIVES ANY RIGHTS IT MAY HAVE THEREUNDER, AS WELL AS UNDER ANY OTHER STATUTES OR COMMON LAW PRINCIPALS OF SIMILAR EFFECT.

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Tenant's Initials

9.2.2 Tenant acknowledges that security devices and services, if any, while intended to deter crime, may not in given instances prevent theft or other criminal acts. Landlord shall not be liable for injuries or losses caused by criminal acts of third parties, and Tenant assumes the risk that any security device or service may malfunction or otherwise be circumvented by a criminal. If Tenant desires protection against such criminal acts, then Tenant shall, at Tenant's sole cost and expense, obtain appropriate insurance coverage.

9.3 Landlord Indemnification. Landlord agrees, subject to the limitations set forth in Section 9.2 and elsewhere in this Lease, to indemnify Tenant and hold it harmless from any and all Claims caused by the gross negligence or willful misconduct of Landlord and/or any of Landlord's Agents or

caused by the willful breach of this Lease by Landlord. The obligations of Landlord under this Section 9.3 shall survive the termination of this Lease with respect to any Claims or liability arising in connection with any event, condition or circumstance occurring, arising or existing prior to such termination. Notwithstanding Landlord's indemnification obligations under this Section 9.3, Landlord shall under no circumstances be liable for loss of profits or special, incidental or consequential damages arising therefrom.

9.4 Claims for Indemnification. If any indemnitee under Sections 9.1 or 9.3 above (an "***Indemnitee***") shall believe that such Indemnitee is entitled to indemnification pursuant to this Article 9 in respect of any Claims, such Indemnitee shall give the appropriate indemnifying party (each, as applicable, an "***Indemnifying Party***") prompt written notice thereof. Any such notice shall set forth in reasonable detail and to the extent then known the basis for such claim for indemnification. The failure of such Indemnitee to give notice of any claim for indemnification promptly shall not adversely affect such Indemnitee's right to indemnity hereunder, except to the extent that such failure adversely affects the right of the Indemnifying Party to assert any reasonable defense to such claim.

9.5 Defense of Claims. In connection with any Claim which may give rise to indemnity under this Article 9 resulting from or arising out of any claim or proceeding against an Indemnitee by a person that is not a party hereto, the Indemnifying Party shall (unless such Indemnitee elects not to seek indemnity hereunder for such claim), upon written notice to the relevant Indemnitee, assume the defense of any such claim or proceeding. The Indemnifying Party shall select counsel reasonably acceptable to such Indemnitee to conduct the defense of such claim or proceeding, shall take all steps necessary in the defense or settlement thereof and shall at all times diligently and promptly perform resolution thereof. Without the prior written consent of the Indemnitee, which consent shall not be unreasonably withheld, conditioned or delayed, the Indemnifying Party will not enter into any settlement of any claim or proceeding which would lead to liability or create any financial or other obligation on the part of the Indemnitee for which the Indemnitee is not entitled to indemnification hereunder. Without the prior written consent of the Indemnifying Party, which consent shall not be unreasonably withheld, conditioned or delayed, the Indemnitee will not enter into any settlement of any claim or proceeding which would lead to liability or create any financial or other obligation on the part of the Indemnifying Party unless the Indemnifying Party has failed or refused to acknowledge responsibility for or defend such claim or proceeding within a reasonable period of time after notice is provided pursuant to Section 9.4.

ARTICLE 10

Insurance

10.1 Landlord's Insurance Landlord shall maintain (subject to Tenant's obligation to pay for such insurance to the extent required under Section 10.2) a policy or policies of insurance protecting Landlord against the following:

10.1.1 Fire and other perils normally included within the classification of fire and extended coverage, together with insurance against vandalism and malicious mischief, to the extent of the full replacement cost of the Premises (including, without limitation, any real property and/or fixture improvements located within the Premises existing as of the Punchlist Sign-off Date), but exclusive of equipment and improvements insured by Tenant, with agreed value, full replacement and such other endorsements Landlord elects to maintain. Landlord may also maintain earthquake and flood coverage if available at commercially reasonable rates.

10.1.2 Eighteen (18) months of rental loss insurance and to the extent of 100% of the gross rentals from the Premises.

10.1.3 Comprehensive general liability insurance with a single limit of not less than $1,000,000 for bodily injury or death and property damage with respect to the Premises, a general aggregate not less than $2,000,000 for bodily injury or death and property damage with respect to the Premises, and not less than $2,000,000 of excess umbrella liability insurance.

10.1.4 At Landlord's sole option, environmental liability or environmental clean-up/remediation insurance in such amounts and with such deductibles and other provisions as Landlord may determine in its sole and absolute discretion.

10.1.5 Such additional insurance as is required under Section 4 of the Work Letter, payment of which shall be considered a Disbursement.

10.2 Payment. Within sixty (60) days after the Term Commencement Date, and within sixty (60) days after the beginning of each calendar year during the period from and after the Term Commencement Date until the termination or expiration of the Lease Term, Landlord shall provide Tenant with a written estimate for such calendar year of the cost of insurance obtained by Landlord with regard to the Premises ("***Insurance Costs***"), which cost may be determined as a percentage of Landlord's portfolio wide insurance policies or other reasonable allocation (for example, based on square footage, insured values or invoiced amounts from insurance carriers or brokers). Tenant shall pay such estimated amount to Landlord in advance in equal monthly installments. Within ninety (90) days after the end of each calendar year, Landlord shall furnish to Tenant a statement showing in reasonable detail the actual costs incurred by Landlord for Insurance Costs for the Premises during such year (the "***Annual Statement***"), and Tenant shall pay to Landlord the costs incurred in excess of the payments previously made by Tenant within thirty (30) days of Tenant's receipt of the Annual Statement. To the extent that any such insurance is maintained pursuant to a blanket or similar policy of insurance, then the cost thereof shall be equitably allocated to the Premises by Landlord.

10.3 Tenant's Insurance. Tenant shall maintain in force, at its sole cost and expense, a policy or policies of insurance protecting Landlord and Tenant against each of the following:

10.3.1 During the Lease Term, comprehensive general liability insurance with respect to the Premises insuring against bodily injury or death and property damage in amounts (i) not less than $2,000,000 in the aggregate, (ii) not less than $1,000,000 per occurrence and (iii) not less than $4,000,000 of excess umbrella liability insurance. Landlord, BioMed Realty, L.P., BioMed Realty Trust, Inc. and any third party now or hereafter providing financing to Landlord where such third party has a security interest in the Premises under such financing shall be included as additional insureds. The amount of such public liability insurance shall be increased from time to time as Landlord may reasonably determine. All such bodily injury and property damage insurance shall insure the performance by Tenant of the indemnity agreement as to personal injury or property damage contained in Section 9.1.

10.3.2 During the Lease Term, insurance covering construction, alterations, additions or improvements permitted under Section 6, trade fixtures and personal property and for those items listed on Exhibit 'C' attached hereto (as the same may be updated by Tenant in accordance with Section 13.1), in an amount not less than 100% of their full replacement cost from time to time during the term of this Lease, providing protection against any peril included within the classification "***fire and extended coverage***," for the repair or replacement of the property damaged or destroyed unless this Lease shall terminate pursuant to Section 20 hereof.

10.3.3 All policies of insurance to be provided by Tenant shall be issued by insurance companies, with general policy holder's rating of not less than A- and a financial rating of not less than Class VII as rated in the most current available "Best's" Insurance Reports, and admitted to do business in the State of California. Such policies shall be issued in the name of Tenant, with Landlord included as an additional insured. The policies provided by Tenant shall be for the mutual and joint benefit and protection of Landlord and Tenant, and

executed copies of such policies of insurance or certificates thereof shall be delivered to the Landlord within ten (10) days after the Term Commencement Date and, thereafter, within thirty (30) days prior to the expiration of the term of each such policy. All public liability and property damage policies shall contain a provision that the Landlord, although an additional insured, shall nevertheless be entitled to recover under said policies for any loss occasioned to it or Landlord's Agents by reason of the negligence of the Tenant. Upon the expiration or termination of any such policy, renewal or additional policies shall be procured and maintained by the Tenant to provide the required coverage. All policies of insurance delivered to Landlord must contain a provision that the company writing said policy will provide Landlord with thirty (30) days notice in writing in advance of any cancellation or lapse or the effective date of any reduction in the amounts of insurance (except in the event of non-payment of premium, in which case ten (10) days written notice shall be given). All public liability, property damage and other casualty policies shall be written as primary policies, not contributing with and not in excess of coverage which Landlord may carry. Tenant agrees that if, after the Term Commencement Date, Tenant does not take out and maintain the insurance required under this Section 10.3, Landlord may (but shall not be required to) procure said insurance on Tenant's behalf, and any costs or expenses incurred by Landlord in connection therewith shall promptly be paid by Tenant to Landlord as Additional Rent.

10.3.4 Notwithstanding anything to the contrary, Tenant's obligation to carry the insurance described in this Section may be brought within the coverage of a so-called blanket policy or policies of insurance carried and maintained by the Tenant, provided that (i) Landlord will be an additional insured thereunder as its interests may appear, (ii) the coverage afforded Landlord will not be reduced or diminished by reason of the use of such blanket policy of insurance, and (iii) the requirements set forth herein are otherwise satisfied. Tenant agrees to permit Landlord at all reasonable times to inspect the policies of insurance of Tenant covering the Premises for policies which are not required to be delivered to Landlord.

10.4 Release of Subrogation Rights. Landlord and Tenant hereby mutually release each other from liability and waive all right to recover against each other for any loss from perils insured against under their respective insurance policies, including any extended coverage and special form endorsements to said policies; provided, however, this Section shall be inapplicable if it would have the effect, but only to the extent that it would have the effect of invalidating any insurance coverage of Landlord or Tenant. The parties shall obtain, if available, from their respective insurance companies, a waiver of any right of subrogation which said insurance company may have against the Landlord or the Tenant, as the case may be.

ARTICLE 11

Repairs and Maintenance

11.1 Maintenance of Premises and Equipment. During the Lease Term, Tenant, at its sole cost and expense, shall maintain and keep the Premises, all improvements thereon, and all appurtenances thereto, including, without limitation, sidewalks, parking areas, curbs, roads, driveways, lighting standards, landscaping, sewers, water, gas and electrical distribution systems and facilities, drainage facilities, and all signs, both illuminated and non-illuminated, in each case whether now or hereafter on the Premises, in good condition and in a manner consistent

with the Permitted Use. During the Lease Term, Tenant shall make all repairs, replacements and improvements required to so maintain in good condition the Premises, including, without limitation, all roof or other structural repairs, HVAC, plumbing, mechanical systems and electrical repairs, replacements and improvements required, and shall keep the same free and clear from all rubbish and debris. All repairs made by Tenant shall be at least equal in quality to the original work, and shall be made only by a licensed, bonded contractor approved in advance by Landlord (which approval shall not be unreasonably withheld, conditioned or delayed); provided, however, that such contractor need not be bonded or approved by Landlord if the alterations, repairs, additions or improvements to be performed are non-structural and the cost of same will not exceed Fifty Thousand Dollars ($50,000) per occurrence or an aggregate amount of One Hundred Thousand Dollars ($100,000) in any twelve (12) month period. Tenant shall not take or omit to take any action, the taking or omission of which could cause waste, damage or injury to the Premises. Tenant shall indemnify Landlord as further specified in Sections 9.1, 9.4 and 9.5.

11.2 Maintenance of Exteriors. Without limiting the effect of Section 11.1, during the Lease Term, Tenant shall maintain the lines designating the parking spaces in good condition and paint the same as often as may be necessary, so that they are easily discernable at all times; resurface the parking areas as necessary to maintain them in good condition; paint any exterior portions of the Building Improvements as necessary to maintain them in good condition; maintain the roof and landscaping in good condition; maintain sightly screens, barricades or enclosures around any waste or storage areas; and take all reasonable precautions to ensure that the drainage facilities of the roof are not clogged and are in good and operable condition at all times.

11.3 No Abatement. There shall be no abatement of Rent and no liability of Landlord by reason of any injury to or interference with Tenant's business arising from the Tenant's (or Landlord's if Landlord elects to make repairs, maintenance, alterations or improvements as explicitly permitted by this Lease) making of any repairs, alterations or improvements in or to any portion of the Premises, or in or to improvements, fixtures, equipment and personal property therein.

11.4 Right of Entry. Landlord, Landlord's Agents and any contractor or consultant of Landlord shall have the right to enter upon the Premises or any portion thereof in accordance with the terms and conditions of Article 15 for the purposes of performing any repairs or maintenance Landlord is permitted to make pursuant to this Lease, and of ascertaining the condition of the Premises or whether Tenant is observing and performing Tenant's obligations hereunder, all without interference from Tenant or Tenant's Agents.

11.5 Compliance with Governmental Regulations. From and after the Term Commencement Date, Tenant shall, at its sole cost and expense, promptly and properly observe and comply with, including the making by Tenant of any Tenant Alterations to the Premises, all present and future orders, regulations, directions, rules, laws ordinances, and requirements of any Governmental Authority, arising from the use or occupancy of, or otherwise applicable to, the Premises.

11.6 Service Contracts. Except to the extent self-performed by Tenant's qualified and experienced personnel, as reasonably determined by Landlord, from and after the Term Commencement Date, Tenant shall, at Tenant's sole cost and expense, procure and maintain contracts, with copies to Landlord, in customary form and substance for, and with contractors specializing and experienced in the maintenance of the following equipment and improvements, if any, if and when installed on the Premises: (i) HVAC equipment, (ii) boiler, and pressure vessels, (iii) fire extinguishing systems, including fire alarm and/or smoke detection, (iv) landscaping and irrigation system, (v) roof covering and drains, (vi) clarifiers, (vii) basic utility feed to the perimeter of the Building Improvements, and (vii) any other equipment (if reasonably required by Landlord). However, Landlord reserves the right, upon notice to Tenant, to procure and maintain any or all of such service contracts, and if Landlord so elects, Tenant shall reimburse Landlord, upon demand, for the cost thereof.

11.7 Action by Landlord if Tenant Fails to Maintain. From and after the Term Commencement Date, Landlord shall not be required to maintain or make any repairs or replacements of any nature or description whatsoever to the Premises, except for completion of Punchlist Items. Tenant hereby expressly waives the right to make repairs at the expense of Landlord as provided for in any Applicable Laws in effect as of the Effective Date, or in any other Applicable Laws that may hereafter be enacted, and Tenant further waives its rights under Applicable Laws relating to a landlord's duty to maintain the Premises in a tenantable condition; provided, however, that this Section 11.7 shall not limit Tenant's express rights under Section 19.3.1 of this Lease (solely with respect to Landlord's obligations under Articles 20 and 21, and Landlord's obligation to complete the Punchlist Items). Notwithstanding the foregoing, if Tenant refuses or neglects to repair, maintain, alter or improve the Premises, in each case as required by the provisions of this Lease to the reasonable satisfaction of Landlord, Landlord, at any time following ten (10) days from the date on which Landlord shall make written demand on Tenant to effect such repair, maintenance, alteration or improvement (except in the event of an emergency, in which case no prior written demand is required), may (in addition to any other remedies available to Landlord under this Lease), but shall not have the obligation to, make such repair and/or maintenance and/or alteration and/or improvement with qualified and experienced contractors (without liability to Tenant for any loss or damage which may occur to Tenant's merchandise, fixtures or other personal property, or to Tenant's business by reason thereof) and Tenant shall pay to Landlord as Additional Rent, within five (5) days following Tenant's receipt of Landlord's invoice therefor, Landlord's costs for making such repairs, maintenance, alteration or improvement plus interest at the Default Rate from the date such costs were incurred by Landlord. Moreover, Tenant's failure to pay any of the charges in connection with the performance of its maintenance and repair obligations under this Lease will constitute a material default under the Lease.

ARTICLE 12

Taxes

12.1 Tenant shall pay the following taxes:

12.1.1 Personal Property Taxes. Tenant shall pay prior to delinquency all taxes, assessments, license fees, and other public charges levied, assessed or imposed or which become payable upon Tenant's personal property, including, but not limited to Tenant's furnishings, movable equipment and all other personal property installed or located in the Premises. Whenever possible, Tenant shall cause said furnishings, movable equipment and personal property to be separately assessed. If, however, any or all of said items shall be assessed and taxed with the real property, Tenant shall pay to Landlord such taxes as are attributable to Tenant's furnishings, movable equipment and personal property within fifteen (15) days after receipt of an invoice from Landlord advising Tenant of the taxes applicable to Tenant's property.

12.1.2 Real Property Taxes. During the Lease Term, Tenant shall also pay at least twenty (20) days before delinquent any and all Real Estate Taxes, assessed or imposed, or which become a lien upon or become chargeable against or payable in connection with the Building Improvements and the Premises. Within three business days of such payment, Tenant shall provide Landlord evidence of such payment in a form reasonably acceptable to Landlord. In the event that the Premises are not separately assessed, Tenant shall pay an equitable proportion of the Real Estate Taxes and assessments for all the land and improvements included within the tax parcel(s) assessed, with such proportion to be determined by Landlord from the respective valuations assigned in the Assessor's worksheets and such other information as is reasonably available to Landlord, including the Building Improvements and any special improvements constructed for the benefit of Tenant. Real Estate Taxes for the last year of the term of this Lease shall be prorated between Landlord and Tenant as of the expiration date of the term. With respect to any assessments which may be levied against or upon the Building Improvements or the Premises, or which under the laws then in force may be evidenced by improvement or other bonds and may be paid in annual installments, only the amount of such annual installment, with appropriate proration for any partial year, and interest thereon, shall be included within a computation of taxes and assessments levied against the Building Improvements or the Premises. To the extent tax bills are not otherwise delivered to Tenant and such tax bills are delivered to Landlord, at least sixty (60) days prior to the applicable delinquency date, Landlord will provide Tenant with written notice detailing the amount and due date of each real estate tax Tenant is required to pay pursuant to this Section 12.1.2. In the event that Tenant incurs a late charge on the payment of the Base Monthly Rental or fails to pay the real property taxes within twenty (20) days before delinquent, Landlord may estimate the current real property taxes, and require that such taxes be paid in advance to Landlord by Tenant monthly in advance with the payment of the Base Monthly Rental. Such monthly payment shall be equal to the amount of the estimated installment of taxes divided by the number of months remaining before the month in which such installment becomes delinquent. When the actual amount of the applicable tax bill is known, the amount of such equal monthly advance payments shall be adjusted as required to provide the funds needed to pay the applicable taxes. If the amount collected by Landlord is insufficient to pay such Real Estate Taxes when due, Tenant shall pay Landlord, upon demand, such additional sum as is necessary. Upon receipt of the full amount of the Real Estate Taxes for such period, Landlord shall, if practicable, pay such Real Estate Taxes before they are delinquent. Advance payments may be intermingled with other moneys of Landlord and shall not bear interest. In the event of a breach by Tenant in the performance of its obligations under this Lease, then any such advance payments may be treated by Landlord as an additional security deposit; provided, however, to the extent that Landlord applies such payments to anything other than real estate taxes, then Landlord shall promptly give Tenant notice of such application.

12.2 Definition of Taxes. For purposes of this Lease, "***Real Estate Taxes***" shall include, without limitation, each of the following (subject to the provisions of Section 12.3.7):

12.2.1 Any form of assessment, license fee, license tax, bond or improvement bond, business license tax, commercial rental tax, levy, charge, penalty, or tax, imposed by any authority having the direct power to tax, including any city, county, state or federal government, or any school, agricultural, lighting, drainage or other improvement or special district thereof, as against any legal or equitable interest of Landlord in the Premises or the real property of which the Premises constitute a part;

12.2.2 Any tax on Landlord's right to rent or other income from the Premises or as against Landlord's business of leasing the Premises, or taxes on or measured by gross rentals received from the rental of space on the Premises;

12.2.3 Any assessment, tax, fee, levy or charge in substitution, partially or totally, of any assessment, tax, fee, levy or charge previously included within the definition of real property tax, it being acknowledged by Tenant and Landlord that Proposition 13 was adopted by the voters of the State of California in the June 1978 election and that assessments, taxes, fees, levies and charges may be imposed by governmental agencies for such services as fire protection, street, sidewalk and road maintenance, refuse removal and for other governmental services formerly provided without charge to property owners or occupants. It is the intention of Tenant and Landlord that all such new and increased assessments, taxes, fees, levies and charges and all similar assessments, taxes, fees, levies and charges be included within the definition of real property tax for purposes of this Lease;

12.2.4 Any tax allocable to or measured by the area of the Premises or the rental payable hereunder, including without limitation, any gross income tax or excise tax levied by the State, any political subdivision thereof, city, or federal government, with respect to the receipt of such rental, or upon or with respect to the possession, leasing, operating, management, maintenance, alteration, repair, use of occupancy by Tenant of the Premises, or any portion thereof;

12.2.5 Any tax upon this transaction or any document to which Tenant is a party, creating or transferring an interest or an estate in the Premises; and

12.2.6 Any tax, fee, levy, assessment or charge, or any increase therein imposed by reason of events occurring during the Lease Term (including but not limited to, any tax, fee, assessment or charge under California Proposition 13 resulting from a change in the ownership of the Premises or any entity owning a direct or indirect interest in the Premises).

12.2.7 Notwithstanding anything contained in this Lease, "Real Estate Taxes" shall not include Landlord's federal or state income, franchise, inheritance or estate taxes.

12.3 Tax Credits. If Landlord receives any tax credits resulting from the Premises, including but not limited to any tax credits resulting from the construction of the Building Improvements, then such tax credits will, as determined by Landlord, be applied either (a) to reduce the amount of Real Estate Taxes payable by Tenant hereunder, or (b) in the PO Model as a cash inflow for consideration in the calculation.

ARTICLE 13

Property Ownership

13.1 Property Ownership. Except for those items listed on Exhibit 'C' (which Exhibit may be updated by Tenant from and after the Term Commencement Date, but in each case only upon receipt of Landlord's prior written approval of such updates in accordance with the procedures set forth at the end of this Section 13.1), and subject to Tenant's Purchase Options under Section 24.2, all of the Building Improvements, and any other improvements, buildings, building systems, equipment, fixtures, machinery, additions and decorations in each case that are paid for (in whole or in part) by Landlord, or that are built into or attached to the Premises, including, without limitation, all installed flooring and installed wall coverings, built-in cabinet work and paneling, sinks and related plumbing fixtures, laboratory benches, exterior venting fume hoods, walk-in freezers, walk-in refrigerators, ductwork, conduits, electrical panels and circuits shall (unless Landlord elects otherwise in writing prior to such construction or installation) automatically become the property of Landlord upon their acquisition or installation at the Premises (regardless of whether the same are installed or paid for by Tenant). All of the foregoing improvements (*except* for those items listed on Exhibit 'C') shall remain upon and be surrendered with the Premises as a part thereof upon the expiration or termination of this Lease. In addition to the foregoing, all materials ordered in connection with the Building Improvements, or under contracts relating to the construction or maintenance of the Building Improvements, shall automatically become the property of Landlord, regardless of whether such materials have been installed at the Premises. Unless this Lease terminates under Section 24.2.9, the Premises shall at all times remain the property of Landlord, and shall be surrendered to Landlord upon the expiration or earlier termination of this Lease in accordance with its terms. Following the Term Commencement Date, and prior to the commencement of any work relating to any Tenant Alterations occurring thereafter, Tenant shall have the ability to update Exhibit 'C' (subject to Landlord's prior written approval in accordance with this Section 13.1) by submitting such updated Exhibit 'C' to Landlord at least twenty (20) days prior to the installation at the Premises of any items requested to be included on Exhibit 'C' by Tenant. Within twenty (20) days of Landlord's receipt of Tenant's updated Exhibit 'C', Landlord shall notify Tenant whether or not Landlord approves the updated Exhibit 'C.' If Landlord fails to respond within such twenty (20) day period, Tenant shall provide a written reminder notice to Landlord. Landlord's failure to respond to such reminder notice within ten (10) days after delivery of such reminder notice shall be deemed approval by Landlord of the updated Exhibit 'C' as submitted to Landlord. Landlord shall be permitted to disapprove additions to Exhibit 'C' only if such items fall into one of the following categories: (i) the item was paid for (in whole or in part) by Landlord; (ii) the item is replacing an item previously paid for (in whole or in part) by Landlord; (iii) the item comprises a part of the building systems or is otherwise necessary for the operation of the Building; or (iv) the item cannot be removed without materially damaging the Building.

13.2 Trade Fixtures. Following the Term Commencement Date, Tenant may install trade fixtures, machinery or other trade equipment in conformance with Article 6 and Section 13.1 of this Lease and Applicable Laws; provided that such trade fixtures, machinery or other trade equipment shall be deemed Landlord's property upon installation and shall not be removed from the Premises at any time unless such items are listed on Exhibit 'C' in accordance with Section 13.1.

ARTICLE 14

[Intentionally Deleted]

ARTICLE 15

Entry by Landlord

15.1 Entry by Landlord. Following the Substantial Completion Date, Tenant shall permit Landlord and Landlord's Agents, and, if accompanied by a representative of Tenant, prospective purchasers, lenders, investors and contractors, to enter the Premises at all reasonable times, upon giving Tenant a forty-eight (48) hour notice, except in the event of an emergency or following an Event of Default, in which case neither notice nor the presence of a representative of Tenant is required, for the purpose of: (i) inspecting the Premises, (ii) performing any of Tenant's obligations under this Lease, (iii) posting notices of non-responsibility with regard to any work, materials, construction, alterations, additions, or repairs, (iv) completing any remaining Punchlist Items, or (v) as permitted under Section 11.4. At all times Landlord or Landlord's Agents are on the Premises, representative(s) of Tenant will have the right to accompany Landlord or Landlord's Agents. Tenant shall timely make a representative of Tenant available to accompany Landlord during any such entry.

15.2 Entry to Relet Premises. Landlord may, during reasonable business hours within eighteen (18) months prior to the expiration of the Lease Term, enter the Premises for the purpose of allowing prospective tenants to view the Premises; provided, however, that Landlord may not exercise such right if Tenant has validly exercised its Purchase Option under this Lease and so long as no breach or condition exists under this Lease or under the Purchase and Sale Agreement which could reasonably be expected to preclude Tenant from consummating its acquisition of the Premises pursuant to such Purchase Option.

15.3 No Liability. Landlord shall be permitted to enter the Premises for any of the purposes stated in and in accordance with Sections 15.1 and 15.2 above without any liability to Tenant for any loss of occupation or quiet enjoyment of the Premises resulting therefrom. In no event shall Tenant's Rent abate as a result of Landlord's activities pursuant to this Article 15.

ARTICLE 16

Assignment and Subletting

16.1 Assignment and Subletting.

16.1.1 Assignment. Except as hereinafter expressly permitted, Tenant shall not voluntarily nor by operation of law, assign, sell, encumber, pledge or otherwise transfer all or any part of Tenant's leasehold estate hereunder, without Landlord's prior written consent in each instance, which consent shall not be unreasonably withheld. Any purported assignment contrary to these provisions shall be void. Landlord's consent shall be based upon a determination that the same (or better) type, class, nature and quality of business, service, management, and

financial soundness of ownership shall exist after such assignment and, provided further, that each and every covenant, condition or obligation imposed upon Tenant by this Lease is assumed by such assignee and each and every right, remedy or benefit afforded Landlord by this Lease is not thereby impaired or diminished. Consent by Landlord to one or more assignments of this Lease shall not operate to exhaust Landlord's rights under this Section.

16.1.2 Subletting. Except as hereinafter expressly permitted (including as permitted under Section 16.3), Tenant shall not sublet any portion of the Premises, and shall not enter into any arrangement that is the functional (if not legal) equivalent of a sublease, without Landlord's prior written consent in each instance, which consent shall not be unreasonably withheld, conditioned or delayed; provided, (a) Tenant may sublet up to an aggregate amount of 25,000 square feet of space at the Premises to or by any person(s) or entity(ies) (each, a "***Permitted Sublease***") and (b) Tenant may sublet the Premises, or any portion thereof, to any (i) corporation or other entity which controls, is controlled by, or is under common control with Tenant; or (ii) a "satellite company" of Tenant (as described in Tenant's Annual Report on Form 10-K for the year ended December 31, 2009) (a "***Tenant Affiliate***") (any such sublease, an "***Exempt Sublease***"). Upon the effectuation of a Permitted Sublease or an Exempt Sublease, Tenant will promptly notify Landlord regarding such sublet or other occupancy right granted by Tenant with regard to the Premises, and the size and location of the space relating thereto. No Permitted Sublease or Exempt Sublease shall specify a term which extends beyond the Lease Term, and all Permitted Subleases and Exempt Subleases shall explicitly state that they are subject and subordinate to this Lease. Any purported subletting of the Premises or other occupancy agreement that is contrary to the provisions of this Section 16.1.2 shall be void. Landlord's consent shall be based upon a determination that the same (or better) type, class, nature and quality of business, service, management, and financial soundness of ownership shall exist after such subletting or other occupancy agreement (taking into account that Tenant shall remain liable for all obligations of Tenant under the Lease as set forth in Section 16.4) and, provided further, that each and every covenant, condition or obligation imposed upon Tenant by this Lease is assumed by such subtenant and each and every right, remedy or benefit afforded Landlord by this Lease is not thereby impaired or diminished. Consent by Landlord to one or more sublettings of the Premises shall not operate to exhaust Landlord's rights under this Section.

16.2 Notice to Landlord. If Tenant desires at any time to assign this Lease pursuant to Section 16.1.1 or to sublet the Premises pursuant to Section 16.1.2, it shall first notify Landlord of its desire to do so and shall submit in writing to Landlord (the "***Transfer Notice***"): (i) with respect to a proposed sublease, the size and location of the space Tenant proposes to sublet, (ii) the name of the proposed subtenant or assignee; (iii) the date on which the Tenant proposes that the assignment or sublease be effective, which shall not be earlier than the date which is thirty (30) days after the Transfer Notice (iv) the nature of the proposed subtenant's or assignee's business to be carried on in the Premises; (v) the terms and provisions of the proposed sublease or assignment; (vi) such reasonable financial information as Landlord may request concerning the proposed subtenant or assignee, and (vii) such other information as Landlord may reasonably require. Tenant agrees to reimburse Landlord for Landlord's actual costs and attorneys' fees (not to exceed Five Thousand Dollars ($5000)) incurred in conjunction with the processing and documentation of any requested assignment, subletting, transfer, or change of ownership of this Lease.

16.3 Exempt Assignment. Notwithstanding any provisions of Sections 16.1 to the contrary, Landlord agrees that Tenant may assign its interest in this Lease, without Landlord's prior written consent but with written notice, to any (i) successor by merger or sale of substantially all of Tenant's assets (including, without limitation, this Lease) in a manner such that the assignee will become liable and responsible for the performance and observance of all Tenant's duties and obligations hereunder; or (ii) corporation or other entity which controls, is controlled by, or is under common control with Tenant, provided that (a) Tenant shall notify Landlord in writing at least ten (10) days prior to the effectiveness of such assignment, and (b) the creditworthiness of the assignee measured immediately following such assignment is at least equal to the creditworthiness of Tenant measured immediately prior to such assignment, in each case as reasonably determined by Landlord (any such assignment, an "***Exempt Assignment***"). For purposes of this Section 16.3 and Section 16.1.2 above, a corporation or other entity will be regarded as in control of another corporation or entity if it both (i) owns or controls in excess of fifty percent (50%) of the voting stock or other ownership interest of the other corporation or entity, and (ii) possesses, directly or indirectly, the power to direct or cause the direction of the management and policies of such other corporation or entity.

16.4 No Release of Liability. No subletting or other occupancy agreement or arrangement, even with the consent of Landlord, shall relieve Tenant of its obligation to pay the Rent and perform all the other obligations to be performed by Tenant hereunder. The acceptance of Rent by Landlord from any other person shall not be deemed to be a waiver by Landlord of any provision of this Lease or to be a consent to any assignment or subletting.

16.5 Landlord's Option. Except for Exempt Assignments, Exempt Subleases and Permitted Subleases, if Tenant desires at any time to assign or sublet the Premises, Landlord, within fifteen (15) days after Landlord's receipt of all of the information required in the Transfer Notice, may by written notice to Tenant elect to terminate this Lease as to the entire Premises, except for those provisions that, by their express terms, survive the expiration or earlier termination hereof. If Landlord exercises such option, then Tenant shall have the right to withdraw such Transfer Notice by delivering to Landlord written notice of such election within five (5) days after Landlord's delivery of notice electing to exercise Landlord's option to terminate this Lease. In the event Tenant withdraws the Transfer Notice as provided in this Section, this Lease shall continue in full force and effect. No failure of Landlord to exercise its option to terminate this Lease shall be deemed to be Landlord's consent to a proposed assignment or sublease. In the event the Landlord elects to terminate the Lease and Tenant does not withdraw such Transfer Notice, the Lease shall terminate on the proposed date the transfer or sublease would be effective as specified in the Transfer Notice and Tenant shall have no further obligations with respect to the Premises other than (a) to surrender and vacate the Premises on or before the effective date of termination, and (b) all obligations of Tenant which survive the expiration or termination of this Lease pursuant to the terms hereof (including, without limitation, all indemnity obligations of Tenant under this Lease). After any such election by Landlord, Landlord shall be entitled to re-lease the Premises in Landlord's sole and absolute discretion.

ARTICLE 17

Dispossession

17.1 No Dispossession. If Tenant shall surrender the Premises, or be dispossessed by process of law, or otherwise, Landlord may terminate this Lease, retake possession of the Premises, pursue its remedies provided herein, and any personal property belonging to Tenant and left on the Premises shall, at the option of Landlord, be deemed abandoned. In such case, Landlord may dispose of said personal property in any manner and is hereby relieved of all liability for doing so.

ARTICLE 18

Events of Default

18.1 Events of Default. The occurrence of any of the following shall constitute a breach and material default of this Lease by Tenant (each, an "***Event of Default***"):

18.1.1 The failure of Tenant to pay or cause to be paid when due any Base Monthly Rental, Additional Rent, Rent, taxes, monies, or charges required by this Lease to be paid by Tenant when such failure continues for a period of five (5) business days after written notice thereof from Landlord to Tenant;

18.1.2 The failure of Tenant to perform any term, covenant, condition or obligation, other than payment of Rent, taxes, monies or charges, required by this Lease, and Tenant shall have failed to cure such failure within thirty (30) days after written notice from Landlord; provided, however, that where such failure cannot reasonably be cured within the thirty (30) day period, an Event of Default shall not occur so long as Tenant has commenced such cure within the same thirty (30) day period and diligently thereafter prosecutes the same to completion;

18.1.3 Subject to the notice and cure provisions of Section 18.1.2 above, Tenant causing, permitting, or suffering, without the prior written consent of Landlord, any act when this Lease requires Landlord's prior written consent or prohibits such act;

18.1.4 Failure by Tenant to deliver an estoppel certificate in accordance with the provisions of Section 26.1;

18.1.5 Tenant is in default under any obligation that accrues prior to the Effective Date and is retained by Tenant under a Construction Agreement assigned by Tenant to Landlord, where as a result of such default the applicable contractor has stopped performing (or threatened to stop performing) Landlord's Construction Work under this Lease; and such default is not cured (i) within the cure periods set forth in such Construction Agreement, or (ii) if such Construction Agreement does not specify a cure period, within five (5) days after notice of such default is provided to Tenant by Landlord or the applicable contractor

18.1.6 Any representation or warranty by Tenant contained in Section 36.7 of this Lease or Section 9.10 of the Work Letter, is incorrect as of the Effective Date; or any representation or warranty made by Tenant under Section 26.3 is incorrect as of the date Tenant made such representation or warranty.

18.1.7 To the extent permitted by Applicable Law, any act of bankruptcy caused, suffered or permitted by Tenant. For purposes of this Lease, "***act of bankruptcy***" shall include any of the following:

18.1.7.1 Any general assignment or general arrangement for the benefit of creditors;

18.1.7.2 The filing of any petition by or against Tenant to have Tenant adjudged a bankrupt or a petition for reorganization or arrangement under any law relating to bankruptcy, unless such petition is filed against Tenant and same is dismissed within one hundred twenty (120) days;

18.1.7.3 The appointment of a trustee or receiver to take possession of substantially all of Tenant's assets located in the Premises or of Tenant's interest in this Lease;

18.1.7.4 The dissolution or liquidation of Tenant; or,

18.1.7.5 The attachment, execution or other judicial seizure of substantially all of Tenant's assets located at the Premises or of Tenant's interest in this Lease.

18.2 Three-day Notice. In the event that Landlord issues a three-day notice, notice of abandonment or comparable document by reason of Tenant's breach, and Tenant cures such breach, Tenant agrees to pay to Landlord, the reasonable cost of preparation and delivery of same.

18.3 No Waiver. The acceptance by Landlord of Rent due hereunder after breach by Tenant will not constitute a waiver of such breach, unless a written notice to that effect has been delivered to Tenant.

18.4 Replacement of Statutory Notice Requirements. When this Lease requires service of a notice, that notice shall replace rather than supplement any equivalent or similar statutory notice, including any notices required by Code of Civil Procedure section 1161 or any similar or successor statute. When a statute requires service of a notice in a particular manner, service of that notice (or a similar notice required by this Lease) in the manner required by Section 35.10 shall replace and satisfy the statutory service-of-notice procedures, including those required by Code of Civil Procedure section 1162 or any similar or successor statute.

ARTICLE 19

Remedies Upon Event of Default; Special Termination Rights

19.1 Landlord's Remedies. Upon the occurrence of an Event of Default, Landlord may, at its sole discretion, pursue one or more of the following remedies:

19.1.1 Landlord may, at its option, perform any of Tenant's unfulfilled duties or obligations on Tenant's behalf, including, without limitation, the obtaining of required bonds, insurance policies, governmental licenses, permits or approvals, with Tenant to pay Landlord an amount equal to the costs and expenses incurred by Landlord for such performance, upon receipt of an invoice from Landlord (together with interest thereon at the Default Rate from the date of Landlord's expenditure).

19.1.2 Landlord shall have the remedy in Civil Code section 1951.4, which provides that, when a tenant has the right to sublet or assign (subject only to reasonable limitations), the landlord may continue the lease in effect after the tenant's breach and abandonment and recover rent as it becomes due. Accordingly, if Landlord does not elect to terminate this Lease on account of any Event of Default by Tenant, Landlord may enforce all of Landlord's rights and remedies under this Lease, including the right to recover all Rent as it becomes due;

19.1.3 Landlord, either as an alternative to, or subsequent to, exercising any of its other remedies available to Landlord pursuant to this Lease, may terminate Tenant's right to possession of the Premises by and upon delivery to Tenant of written notice of termination. Landlord may then immediately reenter the Premises and take possession thereof pursuant to legal proceedings and remove all persons and property from the Premises; such property may be removed and stored in a public warehouse or elsewhere at the cost of and for the account of Tenant. No notice of termination shall be necessary in the event that Tenant has abandoned the Premises. In the event that Landlord elects to terminate Tenant's right of possession under this Section 19.1.3, Landlord may recover the following:

19.1.3.1 The worth at the time of the award of the unpaid Rent which had been earned at the time of termination. "***Worth at the time of award***" shall be computed by allowing interest at the Default Rate from the first day the applicable breach giving rise to such Event of Default occurs;

19.1.3.2 The worth at the time of award of the amount by which the unpaid Rent which would have been earned after termination until the time of award exceeds the amount of such rental loss that the Tenant proves could have been reasonably avoided. ***"Worth at the time of award"*** shall be determined by allowing interest at the Default Rate from the first day the applicable breach giving rise to such Event of Default occurs;

19.1.3.3 The worth at the time of award of the amount by which the unpaid Rent for the balance of the Lease Term after the time of award exceeds the amount of such rental loss that the Tenant proves could be reasonably avoided. "***Worth at the time of award***" shall be computed by discounting such amount at the discount rate at the Federal Reserve Bank of San Francisco at the time of award plus one percent (1%); and

19.1.3.4 Any other amount necessary to compensate Landlord for all the detriment proximately caused by Tenant's failure to perform its obligations under the Lease or which in the ordinary course of things would be likely to result therefrom including, but not limited to, commissions and expenses of reletting, attorneys' fees, costs of alterations and repairs, recording fees, filing fees and any other expenses customarily resulting from obtaining possession of leased premises and re-leasing; and

19.1.4 Notwithstanding Section 19.1.3, or anything to the contrary in Section 24.2, if Landlord exercises its right to terminate Tenant's rights to possession of the Premises pursuant to an Event of Default by Tenant (other than for an Event of Default under Sections 18.1.1 or 18.1.7, in which case Tenant shall not have the option to exercise the next available unexpired Purchase Option), then, within five (5) business days following Tenant's receipt of such notice, Tenant may exercise the next available unexpired Purchase Option under Section 24.2 by delivering a Purchase Option Exercise Notice to Landlord within such five (5) business day period. Upon Landlord's receipt of the Purchase Option Exercise Notice, such termination by Landlord shall be ineffective (without limiting any other termination right of Landlord pursuant to this Lease) and, except as set forth below, the procedures set forth in Section 24.2 shall govern such acquisition of the Premises by Tenant. For purposes of clarification, so long as Tenant and Landlord complete the purchase of the Premises by Tenant under this Section 19.1.4, Landlord shall not be entitled to any damages or recoveries under Section 19.1.3 (other than Section 19.1.3.1).

19.1.4.1 If Tenant delivers a Purchase Option Exercise Notice pursuant to this Section 19.1.4 during Lease Years one (1) through ten (10), then (a) the Purchase Option closing date for such accelerated closing shall be the date that is fifteen (15) days after Landlord's receipt of such Purchase Option Exercise Notice (the "***Accelerated Purchase Option Closing Date***"), (b) within five (5) business days of such exercise, Tenant shall provide Landlord with an executed Purchase and Sale Agreement in the form attached as Exhibit 'G' and (c) the purchase price payable by Tenant to Landlord for such Purchase Option shall be calculated as specified in Section 24.2.5, as of the applicable Purchase Option Closing Date, without regard to the fact that such Purchase Option is being exercised earlier than as contemplated by Section 24.2, except that such purchase price specified in Section 24.2.5 is calculated, and PO Model applied, without including any Base Monthly Rental not actually paid by Tenant under this Lease through the Purchase Option Closing Date.

19.1.4.2 If Tenant delivers such Purchase Option Exercise Notice pursuant to this Section 19.1.4 at any time following the tenth (10^{th}) Lease Year, then (a) the Purchase Option closing date for such accelerated closing shall be the Accelerated Purchase Option Closing Date (provided that such Accelerated Purchase Option Closing Date shall be extended to account for any appraisal period required to determine "fair market value" in accordance with clause (c) below), (b) within five (5) business days of such exercise, Tenant shall provide Landlord with an executed Purchase and Sale Agreement in the form attached as Exhibit 'G' and (c) the purchase price payable by Tenant to Landlord for such Purchase Option shall equal the "***fair market value***" (as such value is determined in accordance with Section 24.2.5(b)) for the Premises determined as of the date that is thirty (30) days prior to the Purchase Option Closing Date.

19.1.5 Landlord may pursue any and all other rights or remedies available to Landlord at law or in equity.

19.2 Landlord's Special Termination Rights

19.2.1 Landlord's Termination Right For Entitlements. If (i) as of October 21, 2010, all approvals needed for the Planned Industrial Permit for the Building have not been received or remain subject to any potential appeal or challenge (ii) as of December 2, 2010, the precise grading permit has not been received or remains subject to any potential appeal or challenge, (iii) as of December 25, 2010, the building permit for the construction of the shell and core of the Building has not been received or remains subject to any potential appeal or challenge or (iv) as of April 19, 2011, the building permit for the construction of the Tenant Improvements has not been received or remains subject to any potential appeal or challenge, in each case for any reason other than Landlord's gross negligence or willful misconduct, then Landlord shall have the option (in Landlord's sole discretion) to terminate this Lease upon ten (10) days written notice to Tenant ("***Landlord's Entitlement Termination Right***"). Following the exercise of Landlord's Entitlement Termination Right, (a) the Lease shall be fully and finally surrendered and terminated and shall no longer be of any force or effect, except for those provisions that, by their express terms, survive the expiration or earlier termination of the Lease; and (b) Landlord will immediately return to Tenant any Base Monthly Rental previously paid by Tenant to Landlord under this Lease, plus interest thereon at LIBOR if Landlord has held such Base Monthly Rental payments for longer than twelve (12) months prior to such termination.

19.2.2 Landlord's Termination Right For Techbilt Purchase Option. Under that certain Real Estate Sale and Purchase Agreement and Joint Escrow Instructions (the ***"Techbilt PSA"***) dated February 19, 2010 between Tenant and Techbilt, Techbilt has the right to repurchase the Land under certain circumstances, as more fully described in Section 18.2 of the Techbilt PSA (the ***"Techbilt Repurchase Option"***). If Techbilt exercises its Techbilt Repurchase Option, and Landlord sells the Land to Techbilt under the Techbilt Repurchase Option, then effective immediately prior to the closing of such sale of the Land to Techbilt, this Lease shall automatically be fully and finally surrendered and terminated and shall no longer be of any force or effect, except for those provisions that, by their express terms, survive the expiration or earlier termination of the Lease (a ***"Techbilt Termination Event"***). If a Techbilt Termination Event occurs and the circumstances giving rise to Techbilt's right to exercise the Techbilt Purchase Option were caused by Tenant's negligent acts or omissions (and not caused by Landlord's negligent acts or omissions), then within ten (10) business days of Tenant's receipt of an invoice therefor, Tenant will pay Landlord an amount equal to 50% of the *difference* between (a) the Aggregate Disbursements made by Landlord plus any other costs out-of-pocket incurred by Landlord with respect to this Lease which have accrued as of the Techbilt Termination Event and (b) the aggregate proceeds received by Landlord from such sale pursuant to the Techbilt Repurchase Option; *provided*, in all other circumstances, if a Techbilt Termination Event occurs Landlord will immediately return to Tenant any Base Monthly Rental previously paid by Tenant to Landlord under this Lease, plus interest thereon at LIBOR if Landlord has held such Base Monthly Rental payments for longer than twelve (12) months prior to such termination.

19.3 Landlord Default; Firm Completion Date

19.3.1 Landlord shall not be in default under this Lease unless Landlord fails to perform any of its obligations under this Lease, such failure materially interferes with the Tenant's use and operations within the Premises and Landlord fails to cure such default within twenty (20) days after written notice from Tenant specifying the nature of such default where

such default could reasonably be cured within said twenty (20) day period, or fails to commence such cure within said twenty (20) day period and thereafter fails to continue with due diligence to prosecute such cure to completion where such default could not reasonably be cured with said twenty (20) day period. If a Landlord default occurs, then (1) Tenant may proceed in equity or at law to compel Landlord to perform its obligation and/or to recover damages proximately caused by such failure to perform; and/or (2) Tenant may perform such obligations and have the right to be reimbursed for the sum it actually and reasonably expends in the performance thereof.

19.3.2 If the Substantial Completion Date has not occurred by January 1, 2013 (the ***"Firm Completion Date"***), then Tenant's obligation to pay Base Monthly Rental will be abated down to zero dollars ($0) until such time as the Substantial Completion Date occurs (at which time Tenant will resume paying full Rent in accordance with Article 3); *provided, however* that the Firm Completion Date shall be subject to reasonable extension on account of a Tenant Delay or Force Majeure. As used herein, ***"Tenant Delay"*** shall mean: (1) delays or failure of Tenant to deliver items in accordance with the Work Letter; (2) Tenant's failure to timely fulfill its obligations as set forth in the Lease related to Landlord's Construction Work within the time periods set forth herein; (3) delays caused by Shell and Core Tenant Change Order Requests or TI Tenant Change Order Requests; or (4) a willful or negligent act or omission of Tenant or Tenant's Agents that materially interferes with the progress of the work; provided, however, that if Landlord becomes aware of any event or circumstance constituting a Tenant Delay and does not provide Tenant with notice thereof within five (5) business days after the date on which Landlord becomes aware of such event or circumstance, then any period of time between the date on which such five (5) business day period expires and the date upon which Landlord does provide such notice to Tenant shall not be considered part of such Tenant Delay; provided, further, however, that no such notice and cure period shall be required if such delay is with respect to interference with the Landlord's construction activities and Landlord has previously notified Tenant of similar Tenant Delays.

19.3.3 Notwithstanding the foregoing, Tenant shall have no right to terminate this Lease for any such default by Landlord, and in no event shall Landlord be liable for loss of profits or special, incidental or consequential damages arising from any such default.

19.3.4 Notwithstanding any provision of this Lease to the contrary, if (A) the Substantial Completion Date is delayed as a result of Force Majeure for a period of five (5) years or more after the date upon which Landlord provided notice to Tenant of such Force Majeure; (B) a temporary taking of the Premises, as described in Section 21.4, shall have occurred prior to the Substantial Completion Date and shall have lasted for a period of five (5) years or more and such five (5) year period expires prior to the Substantial Completion Date; or (C) Tenant's obligation to pay Base Monthly Rental has abated down to zero dollars ($) under Section 19.3.2 for a period of five (5) years or more, then, in each case (a) either party may terminate this Lease upon the expiration of such five (5) year period by delivery of written notice of such termination to the other party, and (b) provided that the event giving rise to such Force Majeure, temporary taking or abatement (as the case may be) was not caused by any act or omission of Tenant, upon such termination Landlord will immediately return to Tenant any Base Monthly Rental previously paid by Tenant to Landlord under this Lease, plus interest thereon at LIBOR if Landlord has held such Base Monthly Rental payments for longer than twelve (12) months prior to such termination. Upon any termination under this Section 19.3.4, the Lease shall be fully and finally surrendered and terminated and shall no longer be of any force or effect, except for those provisions that, by their express terms, survive the expiration or earlier termination of the Lease.

ARTICLE 20

Damage or Destruction

20.1 Landlord's Obligation to Rebuild. If the Premises are partially or completely damaged or destroyed by fire or other perils (as opposed to ordinary wear and tear in which case Tenant's obligations under Article 11 shall apply), Landlord shall promptly and diligently rebuild and restore the Premises unless it has the right to terminate this Lease as provided in Section 20.2 below and it elects to so terminate. For purposes of this Section 20.1, "***Premises***" shall include any real property and/or fixture improvements located within the Premises as of the date upon which such damage or destruction occurs, except for those items set forth on Exhibit 'C'. If required pursuant to this Section 20.1, Landlord shall promptly rebuild or restore the Premises to as nearly as possible its condition immediately prior to such destruction or damage, such work (including, without limitation, the hiring of an architect) to be commenced within ninety (90) days from the time of disaster and thereafter to be prosecuted with due diligence until such rebuilding or restoration is completed. Landlord shall have the right to receive the proceeds of all insurance policies maintained by Landlord and Tenant with regard to the Premises and relating to such damage or destruction (except for those proceeds which are (a) payable under policies obtained by Tenant which specifically insure Tenant's personal property and machinery, and (b) are payable with regard to property which Tenant is permitted to remove from the Premises upon the expiration or termination of this Lease pursuant to the provisions of this Lease), and such proceeds shall be deemed the property of Landlord. If Landlord is required to restore the Premises following any damage or destruction pursuant to this Section 20.1, then Landlord shall deposit any insurance proceeds received by Landlord in connection with such damage or destruction (other than proceeds from business interruption or rental abatement insurance paid to cover the interruption of Landlord's business) in a separate account at a bank to be determined by Tenant (provided that such bank shall have a rating of at least "AAA" under the Standard & Poors ratings for financial institutions) and shall grant Tenant a security interest in such account via a deposit account control agreement and a security agreement in form and substance reasonably satisfactory to Landlord to secure the performance by Landlord of its restoration obligations under this Section 20.1.

20.2 Landlord's Right to Terminate. Landlord shall have the right to terminate this Lease following damage to or destruction of the Premises if any of the following occurs: (i) the amount of insurance proceeds (other than proceeds from business interruption or rental abatement insurance paid to cover the interruption of Landlord's business) that have been irrevocably committed (in writing within ninety (90) days following the date of damage) without material condition (except for the right to make progress payments) to be paid to Landlord by Landlord's insurer is insufficient to pay one hundred percent (100%) of the cost to fully repair the damaged Premises (including any real property or fixture improvement thereon, except for those items set forth on Exhibit 'C'), excluding the deductible for which Tenant shall also be responsible (provided, however, in the event of damage or destruction prior to the Substantial

Completion Date Tenant shall not be responsible for any deductible); (ii) the Premises cannot, with reasonable diligence, be fully repaired by Landlord within twenty-four (24) months after the date of the damage or destruction; (iii) the Premises cannot be safely repaired because of the presence of hazardous factors, including, but not limited to, earthquake faults, radiation, chemical waste and other similar dangers; (iv) the Premises are destroyed or damaged during the last twenty-four (24) months of the Lease Term (exclusive of any option periods); or (v) an uncured Event of Default exists at the time of such damage or

destruction. Any Damage Determination Notice delivered pursuant to Section 20.6 shall specify which (if any) of the items described in Sections 20.2(i)-(v) are applicable to such Damage Determination Notice. Notwithstanding the foregoing, if, prior to the Term Commencement Date, Landlord exercises its right to terminate this Lease pursuant to this Section 20.2, and provided that the damage or destruction giving rise to such termination was not caused by Tenant's acts or omissions, then upon such termination Landlord will immediately return to Tenant any Base Monthly Rental previously paid by Tenant to Landlord under this Lease, plus interest thereon at LIBOR if Landlord has held such Base Monthly Rental payments for longer than twelve (12) months prior to such termination.

20.3 Tenant's Right to Terminate. Tenant shall have the right to terminate this Lease following damage to or destruction of the Premises if any of the following occurs: (i) the Premises cannot reasonably be expected to, with reasonable diligence, be fully repaired by Landlord within twenty-four (24) months after the date of the damage or destruction; or (ii) the Premises are destroyed or damaged during the last twenty-four (24) months of the Lease Term.

If a party elects to terminate this Lease pursuant to Section 20 and has the right to so terminate, such party will give the other party written notice of its election to terminate within thirty (30) days after (a) with respect to the Landlord, Landlord's delivery of the Damage Determination Notice under Section 20.6 indicating the satisfaction of the conditions set forth in Section 20.2, and (b) with respect to Tenant, Tenant's receipt of the applicable Damage Determination Notice under Section 20.6 and the satisfaction of the conditions set forth in Section 20.3; and in such case this Lease will terminate fifteen (15) days after receipt of such notice. If this Lease is terminated pursuant to Sections 20.2 or 20.3, Landlord shall, subject to the rights of its lender(s), be entitled to receive and retain all the insurance proceeds resulting from the applicable damage or destruction, except for those proceeds which are (i) payable under policies obtained by Tenant which specifically insure Tenant's personal property and machinery, and (ii) applicable to property that Tenant would be permitted to remove from the Premises upon the expiration or termination of this Lease pursuant to this Lease. If neither party elects to terminate the Lease, Landlord shall, promptly following the date of such damage or destruction and receipt of commitments for the amounts required of Tenant pursuant to Section 20.2(i) above, commence the process of obtaining necessary permits and approvals, and shall diligently commence repair of the Premises as soon as practicable and thereafter prosecute the same diligently to completion, in which event this Lease will continue in full force and effect.

20.4 Limited Obligation to Repair. Landlord's obligation to repair or rebuild in accordance with this Section 20 shall include an obligation to repair or rebuild the Premises (including any real property and/or fixture improvements existing on the Premises as of the time of such damage or destruction, except for those items set forth on Exhibit 'C'). In addition, Tenant shall, at its expense, replace or fully repair all of Tenant's personal property and any

alterations installed by Tenant existing at the time of such damage or destruction that Tenant would otherwise be permitted to remove from the Premises upon the expiration or termination of this Lease pursuant to this Lease; provided, so long as there is no uncured Event of Default caused by Tenant, Landlord will make available to Tenant any portion of insurance proceeds Landlord receives which are allocable to the alterations and property Tenant is obligated to repair under this Section 20.4, with such proceeds to be disbursed according to such procedures and requirements as Landlord shall reasonably specify. Notwithstanding the foregoing, Landlord may, in Landlord's sole discretion, elect to repair or rebuild those items set forth on Exhibit 'C' provided that Tenant assigns, and Tenant shall assign, any insurance proceeds Tenant receives in connection therewith to Landlord, and in any event only to the extent that the cost of such repair or rebuild is covered by such proceeds.

20.5 Abatement of Rent. Rent shall be temporarily abated in proportion to the degree to which Tenant's use of the Premises is impaired, but only to the extent of any proceeds received by Landlord from the rental abatement insurance described in Section 10.1 hereof, during any period when, by reason of such damage or destruction, Landlord and Tenant reasonably determine that there is substantial interference with Tenant's Permitted Use. Such abatement shall commence upon such damage or destruction and end upon substantial completion by Landlord or Tenant (as applicable) of the repair or reconstruction which Landlord or Tenant (as applicable) is obligated or undertakes to do. Except for any abatement available under this Section 20.5, Tenant shall not be entitled to any compensation or damages from Landlord for loss of the use of the Premises, damage to Tenant's personal property or any inconvenience occasioned by such damage, repair or restoration. Tenant hereby waives the provisions of Section 1932(2) and Section 1933(4) of the California Civil Code, and the provisions of any similar law hereinafter enacted.

20.6 Replacement Cost & Timing. The determination in good faith by Landlord of (a) the estimated cost of repair of any damage, (b) the time period required for repair and (c) the information set forth in Sections 20.2(i)-(v) of this Lease shall be communicated to Tenant in writing within ninety (90) days of an event of damage or destruction (such notice, a "***Damage Determination Notice***") and be conclusive for purposes of this Section.

20.7 Standing for Claims. If Landlord has the right to make a Claim against a third party related to the damage or destruction to the Premises caused by such third party, and Landlord has legal standing to file and prosecute such a Claim (but Tenant does not have such standing), then, if requested by Tenant, Landlord shall either (i) file and diligently prosecute such a Claim itself, or (ii) allow Tenant to file in the name of Landlord and diligently prosecute such a Claim on Landlord's behalf provided, in each case, any recoveries arising from such a Claim will (a) first be applied to each parties' costs and expenses incurred in connection with such Claim (which amounts will be allocated pro rata if insufficient to cover the totality of such expenses); (b) to the extent such proceeds are compensation for the damage or destruction to the Premises, such proceeds will be applied to the repair of the Premises in accordance with the procedures set forth in this Section 20; and (c) at the election of Tenant, any remaining proceeds will either be split [***]% to Landlord and [***]% to Tenant (with no application of such proceeds to the PO Model as a cash inflow), or Landlord shall retain [***]% of such proceeds and such [***]% shall be applied in the PO Model as a cash inflow for consideration in the calculation. Each party will execute such other instruments, give such further assurances and perform such acts which are or

may become necessary or appropriate to effectuate and carry out the provisions and intent of this Section 20.7. Notwithstanding the foregoing, Tenant acknowledges that any right that it may have to file such a Claim shall be subordinate to, and may be eliminated by the rights that any insurer may have to file or prosecute such a Claim, including any rights that arise as a matter of law (by subrogation or otherwise) or that may be assigned by Landlord to such insurer. Landlord and Tenant fully expect that Tenant shall have no rights under this Section 20.7 with respect to insurable Claims because under most circumstances any right to file or prosecute such a Claim shall be held by Landlord's insurer or Tenant's insurer. Notwithstanding anything in this Section 20.7, if the provisions of this Section 20.7 would in any way limit or adversely affect the rights of Landlord or Tenant under or with respect to any policy or contract of insurance, then the first section of this Section 20.7 shall not be given effect. Additionally, should Landlord file a Claim at the request of Tenant, Tenant shall reimburse Landlord for all its costs and expenses in connection with such Claim (including internal overhead costs and in-house legal

department costs) in the event Landlord does not recover any award as a result of such Claim or in the event that any recoveries are insufficient to cover Landlord's costs and expenses.

ARTICLE 21

Condemnation

21.1 Total Taking — Termination. If title to all of the Premises or so much thereof is taken for any public or quasi-public use under any statute or by right of eminent domain so that reconstruction of the Premises will not result in the Premises being reasonably suitable (as reasonably determined by Landlord and Tenant) for Tenant's continued occupancy for the Permitted Use pursuant to this Lease, this Lease shall terminate as of the earlier to occur of: (a) the date on which the condemnor takes possession of the portion of the Premises that is subject to the condemnation, or (b) the date on which title to the portion of the Premises that is subject to the condemnation is vested in the condemnor. If a termination occurs under this Section 21.1 before the Term Commencement Date, Landlord will immediately return to Tenant any Base Monthly Rental paid by Tenant to Landlord under this Lease, plus interest at LIBOR if Landlord has held such Base Monthly Rental payments for longer than 12 months prior to such termination.

21.2 Partial Taking. If any part of the Premises is taken and the remaining part after Landlord makes repairs and alterations is reasonably suitable, as reasonably determined by Landlord and Tenant, for Tenant's continued occupancy for the Permitted Use pursuant to this Lease, this Lease shall, as to the part so taken, terminate as of the date that possession of such part of the Premises is taken and the Base Monthly Rental shall be reduced in the same proportion that the floor area of the portion of the Building Improvements so taken (less any addition thereto by reason of any reconstruction) bears to the floor area of the Building Improvements measured immediately prior to such taking. Landlord shall, at its sole cost and expense, make all necessary repairs or alterations to the Building Improvements so as to make the portion of the Building Improvements not taken a complete architectural unit; provided, however, that if such partial taking occurs during the Lease Term, Landlord shall only be required to make such repairs or alterations to the extent of any condemnation proceeds received by Landlord with regard to any such taking (exclusive of any condemnation proceeds relating to any loss or reduction of income to be derived by Landlord with regard to the Premises). Such

work shall not, however, exceed the scope of the work done by Landlord in originally constructing the Building Improvements. Base Monthly Rental due and payable hereunder shall be temporarily abated during such restoration period in proportion to the degree to which Tenant's Permitted Use of Premises is impaired. Each party hereby waives the provisions of Section 1265.130 of the California Code of Civil Procedure allowing either party to petition the Superior Court to terminate in the event of a partial taking of the Building Improvements or the Premises. Notwithstanding the foregoing, if more than twenty-five percent (25%) of the square footage of the Building Improvements which have been completed immediately prior to such taking is taken or sold under such threat, Landlord or Tenant may terminate this Lease as of the earlier to occur of: (a) the date on which the condemning authority takes possession of the portion of the Premises that is subject to the condemnation, or (b) the date on which title to the portion of the Premises that is subject to the condemnation is vested in the condemning authority, in each case provided that Landlord or Tenant, as applicable, delivers written notice of such election to terminate to the other party within twenty (20) days after such party receives notification of the taking or, in the absence thereof, within twenty (20) days after the condemning authority shall have taken possession of such portion of the Premises. If a termination occurs under this Section 21.2 before the Term Commencement Date, Landlord will immediately return to Tenant any Base Monthly Rental paid by Tenant to Landlord under this Lease, plus interest at LIBOR if Landlord has held such Base Monthly Rental payments for longer than 12 months prior to such termination.

21.3 No Apportionment of Award. No award for any partial or entire taking shall be apportioned, it being agreed and understood that Landlord shall be entitled to the entire award for any partial or entire taking. Tenant assigns to Landlord its interest in any award which may be made in such taking or condemnation, together with any and all rights of Tenant arising in or to the same or any part thereof. Any award received by Landlord pursuant to this Article 21 shall be applied in the PO Model as a cash inflow for consideration in the calculation. Nothing contained herein shall be deemed to give Landlord any interest in or require Tenant to assign to Landlord any separate award made to Tenant for the (a) unamortized or undepreciated value of any property that Tenant has the right to remove from the Premises upon the expiration or sooner termination of the Lease Term pursuant to this Lease, (b) interruption of Tenant's business, (c) any relocation and/or business re-establishment benefits, or (d) loss of goodwill. Notwithstanding the foregoing, Tenant shall be entitled to receive an award to the extent of that portion of the award received by Landlord which is directly attributable to unamortized or undepreciated value of any property that Tenant has the right to remove from the Premises upon the expiration or sooner termination of the Lease Term pursuant to this Lease.

21.4 Temporary Taking. No temporary taking of the Premises shall terminate this Lease or give Tenant any right to any abatement of Rent, except to the extent covered by insurance proceeds received by Landlord. Any award made to Tenant by reason of such temporary taking shall belong entirely to Tenant and Landlord shall not be entitled to share therein. Each party agrees to execute and deliver to the other all instruments that may be required to effectuate the provisions of this Section.

21.5 Sale Under Threat of Condemnation. A sale made in good faith by Landlord to any authority having the power of eminent domain, either under threat of condemnation or while condemnation proceedings are pending, shall be deemed a taking under the power of eminent domain for all purposes of this Article 21. Landlord will provide Tenant with as much advance notice as is reasonably practicable regarding any actual or contemplated sale under this Section 21.5.

ARTICLE 22

Surrender of Lease

22.1 Surrender of Lease. The voluntary or other surrender of its interest in this Lease by Tenant or a mutual cancellation of this Lease shall not constitute or result in a merger of any interest, and shall, at the election of Landlord, either terminate all or any then-existing subleases or subtenancies or operate as an assignment to Landlord of any or all of such subleases or subtenancies. Landlord shall exercise its election within thirty (30) days of any such surrender or cancellation.

ARTICLE 23

Attorneys' Fees

23.1 Attorneys' Fees. If either party institutes or is made a party to any action or proceeding to enforce or interpret this Lease, the prevailing party in such action or proceeding shall be entitled to recover all costs and attorneys' fees incurred in connection with such action or proceeding, or any appeal or enforcement of such action or proceeding in proportion to [***], up to a maximum of 100%; *provided*, *however*, that in the case where the prevailing party is awarded any equitable relief, then the prevailing party may recover the full amount of such costs and attorney's fees. For example, if the prevailing party [***] and no equitable relief, but [***], and the prevailing party had two hundred thousand dollars ($200,000) in costs and attorneys' fees, then such prevailing party would be entitled to recover [***] of such costs and attorneys' fees.

ARTICLE 24

Sale of the Premises by Landlord; Purchase Option; ROFN

24.1 Sale of Premises. Notwithstanding any provisions of this Lease to the contrary, Landlord may assign, in whole or in part, Landlord's interest in this Lease and may sell all or part of the Premises. Should Landlord elect to sell the Premises, Landlord agrees to notify Tenant of its intent to do so. Landlord's willingness to notify Tenant is to be considered a courtesy notice only and not an offer to sell, or an obligation of any form on the part of Landlord to sell the Premises to Tenant. This courtesy notice is not to be construed as an option, an offer to negotiate, a right of first refusal, or any other form of agreement that would obligate Landlord to pursue a sale of the Premises to Tenant or in any manner prohibit Landlord from its rights to sell all or part of the Premises as it chooses.

24.2 Purchase Option.

24.2.1 Tenant is hereby granted seven separate options to purchase the Premises from Landlord at the end of the following respective Lease Years: the fifth (5th), sixth

(6th), seventh (7th), eighth (8th), ninth (9th), fifteenth (15th) and twentieth (20th) Lease Year, subject to and in accordance with the terms of this Section 24.2 (each a "***Purchase Option***"). The term "***Lease Year***" as referred to herein shall mean each twelve-month period within the Lease Term commencing upon the Term Commencement Date. Each subsequent Lease Year ends twelve months after the preceding one. The last day of each of the fifth (5th), sixth (6th), seventh (7th), eighth (8th), ninth (9th), fifteenth (15th) and twentieth (20th) Lease Year shall be referred to herein as the "***Purchase Option Closing Date***" for each applicable Purchase Option.

24.2.2 Tenant shall have no right to exercise any Purchase Option, or consummate any acquisition pursuant thereto, (a) during any period when a Tenant default exists and is continuing under this Lease (except as provided in Section 19.1.4), or (b) if this Lease has expired or otherwise been terminated. The rights contained in this Section 24.2 shall be personal to Tenant or to any assignee pursuant to an Exempt Assignment, and shall automatically become null and void upon any transfer or assignment by the Tenant (other than an Exempt Assignment).

24.2.3 If Tenant chooses to exercise any Purchase Option, then (a) the closing date for the purchase of the Premises shall be the respective Purchase Option Closing Date, and (b) Tenant shall deliver written notice to Landlord of Tenant's decision to exercise the Purchase Option (the "***Purchase Option Exercise Notice***") at least ninety (90) days prior to such Purchase Option Closing Date. If Tenant exercises any Purchase Option, but the closing of Tenant's purchase of the Premises does not occur by the Purchase Option Closing Date (for any reason other than due to the material default of Landlord hereunder or under the applicable Purchase and Sale Agreement or a failure of closing conditions for the benefit of Tenant set forth in Section 4 of the Purchase and Sale Agreement), then the Purchase Option exercised by Tenant (and all other Purchase Options under this Lease) shall automatically lapse and be of no further force or effect, and Tenant shall have no further rights under this Section 24.2. Notwithstanding the foregoing, if Landlord has encumbered the title to the Premises in a manner which constitutes a violation of the terms of this Lease, then (unless Tenant previously consented to such encumbrance) the applicable Purchase Option Closing Date shall be automatically extended until such encumbrance is either (i) removed as an encumbrance on title to the Premises, or (ii) insured over by the applicable title company.

24.2.4 Upon Landlord's receipt of the Purchase Option Exercise Notice from Tenant, Landlord and Tenant shall execute a purchase and sale agreement for the Premises substantially in the form attached hereto as Exhibit 'G' (the "***Purchase and Sale Agreement***"). In connection with such purchase and sale, Tenant shall reimburse Landlord for all reasonable and customary costs actually incurred by Landlord in connection with the purchase and sale transaction including, but not limited to, attorneys' fees for outside counsel (provided, however, that Tenant will not be required to reimburse Landlord's attorneys' fees in excess of $25,000 (as such amount shall be adjusted by multiplying $25,000 by the CPI Adjustment Factor described below)). As used herein, the "***CPI Adjustment Factor***" means, as of any date, the greater of (a) the CPI for such date divided by the CPI for the Effective Date; and (b) 1.00. As used herein, "***CPI***" means the United States Department of Labor, Bureau of Labor Statistics "Consumer Price Index" for All Urban Consumers (CPI-U) published for the Los Angeles-Riverside-Orange County, CA, Metropolitan Statistical Area, with a base of 1982-1984 = 100. If the CPI ceases to be published, with no successor index, then the parties shall reasonably agree upon a reasonable substitute index. The CPI for any date means the CPI last published before the calendar month that includes such date.

24.2.5 The purchase price payable by Tenant for the acquisition of the Premises pursuant to the Purchase Option shall be as follows:

(a) With regard to any acquisition of the Premises pursuant to the Purchase Option at the end of Lease Year five (5), six (6), seven (7), eight (8) or nine (9), the purchase price shall be calculated as of the applicable Purchase Option Closing Date as further described on Exhibit 'D' (referred to herein as the "***PO Model***"). For illustrative purposes, a sample calculation of the purchase price pursuant to this Section 24.2.5(a) is also attached hereto as Exhibit 'D'. Furthermore, contemporaneously with the execution of this Lease, the parties will exchange a mutually agreed upon software model in executable Microsoft Excel format. Each party shall receive the software model in compact disc format, and shall hold such compact disc in escrow until a Purchase Option Exercise Notice is delivered, at which point such model shall be utilized to calculate the purchase price at the time of the relevant Purchase

Option Closing Date. Promptly following the [***], the parties will discuss and endeavor to agree upon the applicable purchase price (in accordance with Exhibit 'D') for the Purchase Options at the end of Lease Year five (5), six (6), seven (7), eight (8) and nine (9), and the parties will by written amendment append such purchase prices to this Lease as a new Exhibit. If the parties are unable to agree upon the applicable purchase price, then this Lease shall continue in full force and effect until such purchase price is agreed upon. If the date on which such purchase price is agreed upon is after the applicable Purchase Option Closing Date has passed then the closing shall occur on the date that is thirty days after such purchase price is agreed upon.

(b) With regard to any acquisition of the Premises pursuant to the Purchase Option at the end of Lease Year fifteen (15) or twenty (20), the purchase price shall equal the "***fair market value***" for the Premises determined as of the date that is sixty (60) days prior to the Purchase Option Closing Date. For purposes of this Section 24.2, the "***fair market value***" of the Premises shall be determined by the mutual agreement of Landlord and Tenant. However, if Landlord and Tenant are unable to agree upon such fair market value by the sixtieth (60th) day prior to the Purchase Option Closing Date, then "***fair market value***" shall be determined by a process whereby (i) each party shall select an independent and licensed appraiser (who must be a qualified MAI appraiser) for the Premises (with at least ten (10) years experience appraising properties of similar type, use and location as the Premises) within fifteen (15) days of the sixtieth (60th) day prior to the Purchase Option Closing Date, (ii) each such appraiser shall prepare an appraisal of the Premises within fifteen (15) business days after their selection, (iii) if the appraisals of both appraisers with respect to the Premises differ by an amount equal to or less than five percent (5%) of the higher of the two appraisals, then the average of such appraisals shall be deemed to be the fair market value for the Premises for purposes of this Section 24.2, and (iv) if the appraisals of both appraisers with respect to the Premises differ by an amount that exceeds five percent (5%) of the higher of the two appraisals, then the two (2) selected appraisers shall agree upon the selection of a third appraiser who must be a qualified MAI appraiser (also with at least ten (10) years experience appraising properties of similar type, use and location as the Premises that is unaffiliated with either party hereto and that has not been retained or engaged by either party within the five (5) years preceding such appointment) within fifteen (15) days of the date the second determination is sent in, who shall

prepare an appraisal of the Premises within fifteen (15) business days after his or her selection, and such appraisal shall constitute the binding determination of fair market value for purposes of this Section 24.2; provided, however, that such appraisal may not be greater than the higher of the other appraisals or less than the lower of the other appraisals. If the two appraisers are unable to agree upon the selection of a third appraiser, then either Landlord or Tenant shall be entitled to apply to the presiding judge of the Superior Court of the County of San Diego, California for the selection of a third appraiser who shall be selected from a list of names of experienced appraisers submitted by Landlord or from a list of names submitted by Tenant, as the case may be, unless both Landlord and Tenant submit lists of names, in which case the Court, in its sole discretion, shall select the third appraiser from the lists. The cost of all appraisals performed in accordance with this Section 24.2 shall be paid by Tenant. Such determination of "***fair market value***" determined in accordance with this Section 24.2.5 shall be binding upon the parties.

(c) In addition to the purchase price payable by Tenant pursuant to this Section 24.2.5, as a condition to closing, Tenant shall pay all Rent owing to Landlord as of the applicable Purchase Option Closing Date.

24.2.6 It is the intent of the parties that the "***fair market value***" of the Premises be determined by using the appraisal valuation standards then commonly used by professional appraisers in determining fair market value of biomedical use properties in the state in which the Premises is located. Any appraiser appointed pursuant to this Article 24 shall be instructed to determine independently the fair market value of the Premises in accordance with the definition of the term set forth in this Section 24.2.6.

24.2.7 Time is of the essence in the performance of the parties' respective obligations contained in this Section 24.2.

24.2.8 Landlord and Tenant agree to execute such additional documents, including, without limitation, escrow instructions, and take such further actions, as may be reasonable and necessary to carry out the provisions of this Section 24.2.

24.2.9 Upon the consummation of the Tenant's acquisition of the Premises pursuant to the Purchase Option, this Lease shall terminate, and shall be of no further force or effect, except for those rights, obligations, and liabilities which expressly survive such termination or which have accrued prior to such termination.

24.3 Right of First Negotiation. If at any time during the Lease Term, Landlord decides to sell the Land or the Premises, Landlord shall deliver to Tenant written notice thereof (the "***Sale Notice***"). Tenant may, within ten (10) business days after its receipt of the Sale Notice, elect by written notice to Landlord to negotiate with Landlord to purchase the Premises by delivering written notice to Landlord ("***Tenant's Acceptance Notice***"). Promptly thereafter, the parties shall negotiate in good faith the terms and conditions of such purchase and sale of the Premises. If the parties are unable to agree on mutually acceptable terms and conditions and execute a binding commitment for the purchase and sale of the Premises within sixty (60) days after the date of the Sale Notice ("***Offer Period***"), Landlord shall be deemed to have satisfied its obligation to provide Tenant with the right of first negotiation provided for herein and may offer

to sell the Premises in the open market. If Landlord fails to close on the sale of the Premises with a third party within six (6) months from the expiration of the Offer Period (provided such period shall be extended as necessary to close the transaction if Landlord and such third party are in escrow within the six (6) month period), the right of first negotiation provided for herein shall again apply. Tenant's failure to exercise its right of first negotiation under this Section 24.3 shall not affect any of Tenant's other rights under this Lease.

ARTICLE 25

Quiet Enjoyment

25.1 Quiet Enjoyment. If Tenant is not in breach of its covenants, obligations, representations and warranties set forth in this Lease, Landlord covenants that Tenant shall have peaceful and quiet enjoyment of the Premises without hindrance on the part of Landlord. Landlord will defend Tenant in the peaceful and quiet enjoyment of the Premises against claims of all persons claiming through or under Landlord.

ARTICLE 26

Estoppel Certificates and Financial Statements

26.1 Tenant Estoppel Certificates. Tenant shall at any time during the term of this Lease, within fifteen (15) days of written notice from Landlord, execute and deliver to Landlord a statement in writing certifying to Landlord (and to any other party which Landlord may request) that this Lease is unmodified and in full force and effect or, if modified, stating the nature of such modification. Tenant's statement shall include other details requested by Landlord, such as the date to which Rent and other charges are paid, Tenant's knowledge concerning any uncured defaults with respect to Landlord's obligations under this Lease and the nature of such defaults if they are claimed, and such other matters as Landlord may reasonably request. Any such statement may be relied upon conclusively by any purchaser or lender having an interest in the Premises, or by such other parties as Landlord may identify when Landlord requests the issuance of such statement from Tenant. Tenant's failure to deliver such statements within such time shall be conclusive upon the Tenant that this Lease is in full force and effect, except as and to the extent any modification has been represented by Landlord, and that there are no uncured defaults in Landlord's performance, and that not more than one (1) month's Rent has been paid in advance.

26.2 Landlord Estoppel Certificates. Landlord shall at any time during the term of this Lease, within fifteen (15) days of written notice from Tenant, execute and deliver to Tenant a statement in writing certifying that this Lease is unmodified and in full force and effect or, if modified, stating the nature of such modification. Landlord's statement shall also include the dates to which Rent and other charges are paid in advance, if any, an acknowledgment that there are not, to Landlord's knowledge, any uncured defaults on the part of Tenant hereunder, or specifying such defaults if any are claimed, and such further information with respect to this Lease or the Premises as may be reasonably requested thereon. Any such statement may be relied upon by any encumbrancer of Tenant's interest in the Premises.

26.3 Tenant Financial Statements. Within 120 days after the end of each fiscal year, Tenant shall provide Landlord, upon Landlord's written request, a copy of the audited financial statements that have been provided to the US Securities and Exchange Commission ("***SEC***") or, in the event Tenant is no longer required to deliver such financial statements to the SEC, year-end financial statements, including balance sheets and income statements, reflecting Tenant's current financial condition for such fiscal year that have been prepared in accordance with U.S. GAAP and audited by a nationally or regionally recognized firm of certified public accountants. In the event Tenant is no longer required to deliver such financial statements to the SEC, Tenant will represent and warrant at the time it provides any financial statements, records or information pursuant hereto that all financial statements, records and information furnished by Tenant to Landlord in connection with this Lease were prepared in accordance with U.S. GAAP and comply with the requirements of Rule 10(b)-5 under the Securities Exchange Act of 1934, as amended. Furthermore, in the event that Tenant is no longer required to deliver such financial statements to the SEC, Tenant agrees that it shall promptly furnish to Landlord, from time to time upon Landlord's written request, the most recent audited year-end financial statements reflecting Tenant's current financial condition. For purposes of clarification, so long as Tenant has filed such financial statements with the SEC within the time periods set forth above via the publicly available EDGAR filing system (or any successor publicly available filing system), Tenant shall not be required to separately deliver such financial statements to Landlord pursuant to this Section 26.3.

ARTICLE 27

Subordination and Attornment; Tenant's Right to Record

27.1 Subordination of Lease. This Lease and Tenant's rights under this Lease, other than Tenant's security interest in any insurance proceeds as described in Section 20.1, are and shall be subject and subordinate to any current or future mortgage or ground lease to which Landlord is a party, and to all renewals, modifications, consolidations, replacements, or extensions thereof, now or hereafter affecting the Premises. The provisions of this Section shall be self operative, and no further instrument of subordination shall be required. In confirmation of such subordination, however, Tenant shall within ten (10) days execute and deliver any instruments that Landlord, the holder of any mortgage, or the landlord of any ground lease may request to evidence such subordination. If Tenant fails to execute and deliver any such instruments, Tenant irrevocably constitutes and appoints Landlord as Tenant's special attorney-in-fact to execute and deliver such instruments.

27.2 Attornment to Lender. If the holder of any mortgage, or the landlord of any ground lease affecting the Premises, shall hereafter succeed, by foreclosure or otherwise, to the rights of Landlord under this Lease, Tenant shall attorn to and recognize such successor as Tenant's Landlord under this Lease, and shall promptly execute and deliver any instruments that may be necessary to evidence such attornment, and Tenant hereby irrevocably appoints Landlord as Tenant's special attorney in fact to execute and deliver such instruments on behalf of Tenant should Tenant refuse or fail to do so. Upon such attornment, this Lease shall continue in effect as a direct lease between such successor landlord and Tenant upon and subject to all of the provisions of this Lease. Notwithstanding the foregoing, Tenant's agreement both to subordinate and to attorn, as set forth in this Article, is contingent upon Tenant's receipt of a nondisturbance

agreement from the holder of any encumbrance placed against the Premises, in a recordable, commercially reasonable form, providing that in the event of any foreclosure, sale under a power of sale, ground or master lease termination, or transfer in lieu of any of the foregoing, or the exercise of any other remedy under any such encumbrance, but subject to reasonable exceptions: (i) Tenant's use, possession, and enjoyment of the Premises and its rights under the Purchase Options will not be disturbed and this Lease will continue in full force and effect so long as Tenant is not in default; and (ii) this Lease will automatically become a lease directly between any successor to Landlord's interest, as landlord, and Tenant, as if that successor were the landlord originally named in the lease.

27.3 Memorandum of Lease. Concurrently herewith, the parties shall promptly execute, acknowledge, and deliver duplicate originals of a Memorandum of Lease in form attached hereto as Exhibit 'F' (the "***Memorandum of Lease***"). Either party may record such Memorandum of Lease. Any taxes imposed upon such recording shall be paid by Landlord and treated as a Disbursement under this Lease. If the parties amend this Lease, then the parties shall have the same rights and obligations regarding a memorandum of such amendment as they do for the Memorandum of Lease. Except as provided in this Section 27.3, Tenant shall not file or record any other documents with respect to the Premises.

ARTICLE 28

Holding Over

28.1 Holding Over. If Tenant remains in possession of the Premises after the expiration of the Lease Term without executing a new lease or after Landlord has declared a forfeiture by reason of a default by Tenant, then such holding over shall be construed as a tenancy from month to month, subject to all the conditions, provisions and obligations of this Lease insofar as they are applicable to a month to month tenancy, including the provisions of Article 3, except that the Base Monthly Rental shall be one hundred fifty percent (150%) of the Base Monthly Rental last due, payable monthly in advance. Notwithstanding the foregoing, if Tenant fails to vacate the Premises or Tenant fulfills less than all of its obligations hereunder at the end of the Lease Term, Tenant also shall be liable for all damages incurred by Landlord by reason of the latter's inability to deliver possession of the Premises or any portion thereof to any other person.

ARTICLE 29

Mortgagee Protection

29.1 Mortgagee Protection. In the event of any default on the part of Landlord, Tenant agrees to give notice by registered or certified mail to any beneficiary of a deed of trust or mortgage covering the Premises whose address shall have been furnished to the Tenant and shall offer such beneficiary or mortgagee a reasonable opportunity to cure such default (such cure period not to exceed ninety (90) days after receipt of such notice).

ARTICLE 30

Liability of Successors

30.1 Successor's Liability. The covenants and conditions herein contained shall, subject to the provisions as to assignment, apply to and bind the respective heirs, successors, executors, administrators, and permitted assigns of each party hereto.

ARTICLE 31

Easements

31.1 Easements. Landlord reserves the right, from time to time, to grant such easements, rights, liens, encumbrances and dedications that Landlord deems necessary or desirable, and to cause the recordation of parcel maps and restrictions, so long as such easements, rights, dedications, liens, encumbrances, maps and restrictions do not unreasonably interfere with the Permitted Use of the Premises by Tenant. Should Landlord grant any such easements, rights and dedications, Landlord shall notify Tenant promptly thereafter. Tenant shall sign any documents or instruments to accomplish the foregoing upon request of Landlord, and failure to do so shall constitute a material breach of this Lease. Tenant irrevocably appoints Landlord as Tenant's special attorney in fact to execute and deliver such documents or instructions on behalf of Tenant should Tenant refuse or fail to do so. If Landlord receives any consideration for granting any such easements, rights, dedications, liens, encumbrances, maps and restrictions, such consideration shall be applied in the PO Model as a cash inflow for consideration in the calculation; provided, however, that the parties agree that any funds or other consideration received by Landlord or any of Landlord's Agents in connection with any encumbrances securing or relating to money borrowed by Landlord or Landlord's Agents shall not be applied in the PO Model.

ARTICLE 32

Covenants, Conditions and Restrictions

32.1 Compliance with Covenants, Conditions and Restrictions. In addition to requirements imposed by law, the care of the Premises and conduct of business thereupon, among other things, are restricted or subject to heightened requirements pursuant to the CC&Rs. Tenant has received a copy of all applicable CC&R's prior to its execution of this Lease, and such receipt is acknowledged hereby.

32.2 Associations. During the Lease Term, Tenant shall faithfully observe and comply with the provisions of all applicable CC&R's, and all modifications and additions which may from time to time be enacted pursuant to their terms. Tenant shall similarly observe and comply with all requests, demands and orders otherwise made by any governing associations created under the authority of the CC&R's (the "***Associations***"). Any violation by Tenant of the CC&R's or rightful orders of the Associations created thereby after written notice to Tenant shall be a default under this Lease (subject to the cure provisions of Section 18.1.2, but only to the extent such CC&Rs or orders of the Associations afford such cure period with regard to the applicable matter). However, Landlord will not be responsible to Tenant for the nonperformance of any provisions of such CC&R's by its tenants occupying neighboring properties, if any.

32.3 Association Fees. Following the Term Commencement Date, all payments, charge, dues, and assessments imposed under the authority of the CC&R's and the Associations ("***Association Fees***") shall be the sole responsibility of Tenant, who shall timely pay such Association Fees either directly or to Landlord as Additional Rent. Each payment shall be made promptly on demand throughout the term of this Lease and shall be paid without deduction or offset.

32.4 Carlsbad Oaks North Business Park Owners Association. If Landlord is granted a seat on the Carlsbad Oaks North Business Park Owners Association (the "***Association***"), then, to the extent permitted by the bylaws and rules of the Association, Landlord shall designate Tenant to occupy and vote Landlord's seat; provided, however, that Landlord may replace Tenant as the party occupying such seat following the occurrence of an Event of Default. If Tenant is granted a seat on the Association in lieu of Landlord, the provisions of this Section 32.4 shall apply to such circumstance as well. Landlord and Tenant will each promptly copy the other on communications from the Association that relate to the Premises and any common areas. With respect to any matter to be voted upon by the Association, if within ten (10) business days of Landlord's receipt of a notice describing such matter to be voted upon by the

Association, (i) Landlord notifies Tenant regarding Landlord's preferred vote on such matter, Tenant will cast its vote as directed by Landlord; or (ii) in all other cases, Tenant may cast its vote on such matter in Tenant's sole discretion; provided, that in any event, Landlord shall not vote (or direct Tenant to vote) in favor of any matter to be voted upon by the Association that if adopted would materially alter, reduce or adversely affect any of Tenant's rights or materially enlarge Tenant's obligations under this Lease. Notwithstanding any provision of this Section 32.4 to the contrary, if Landlord has not received ten (10) business days prior notice (or such shorter amount of notice necessary for Landlord, in its sole discretion, to review the matter and provide Tenant with its direction) of a matter to be voted upon by the Association, then Tenant shall, to the extent Tenant has the power to do so under the bylaws and rules of the Association, cause the postponement of such vote until such time as Landlord has been provided with reasonable prior notice of such matter to be voted upon; provided, however, that Tenant shall be permitted to vote on a matter in its discretion even if Landlord has not received ten (10) business days prior notice and has not given direction to Tenant with respect to the vote, if such matter shall not have an adverse effect on Landlord's rights and remedies under this Lease or Landlord's interest in the Premises.

ARTICLE 33

Quitclaim Deed

33.1 Quitclaim Deed. Tenant shall execute and deliver to Landlord on the expiration date or earlier termination of this Lease, promptly on Landlord's request, a quitclaim deed conveying to Landlord any and all interest of Tenant in and to the Premises, in recordable form, unless this Lease terminated under Section 24.2.9.

ARTICLE 34

Hazardous Materials

34.1 Definitions:

34.1.1 Hazardous Materials Laws. "***Hazardous Materials Laws***" means any and all federal, state or local laws, ordinances, rules, decrees, orders, regulations or court decisions relating to hazardous substances, hazardous materials, hazardous waste, toxic substances, environmental conditions on, under or about the Premises, or soil and ground water conditions, including, but not limited to, California Labor Code Section 6382, California Health and Safety Code Section 25249.5, et seq., any amendments to and any regulations promulgated pursuant to the foregoing, and any similar federal, state or local laws, ordinances, rules, decrees, orders or regulations.

34.1.2 Hazardous Materials. "***Hazardous Materials***" means any chemical, compound, substance or other material, including, without limitation, gasoline, diesel, aviation fuels, lubricating oils, solvents and chemicals, that: (i) is defined as a hazardous substance, hazardous material, hazardous waste or toxic substance under any Hazardous Material Law; (ii) is controlled or governed by any Hazardous Materials Law, or gives rise to any reporting, notice or publication requirements thereunder, or gives rise to any liability, responsibility or duty on the part of Tenant or County with respect to any third person thereunder; or (iii) is a flammable or explosive material, asbestos, radioactive material, nuclear medicine material, drug, vaccine, bacterial, virus, hazardous waste, toxic substance, or related injurious or potentially injurious material (by itself or in combination with other materials).

34.2 Tenant's Obligations.

34.2.1 Compliance with Laws. During the Lease Term, Tenant shall strictly comply with, and shall maintain the Premises in compliance with, all Hazardous Materials Laws. Tenant shall obtain and maintain in full force and effect all permits, licenses and other governmental approvals required for Tenant's operations on the Premises under any Hazardous Materials Laws and shall comply with all terms and conditions thereof. At Landlord's request, Tenant shall deliver copies of, or allow Landlord to inspect, all such permits, licenses and approvals. Tenant shall perform any monitoring, investigation, clean-up, removal, detoxification, preparation of closure or other required plans and any other remedial work (collectively, "***Remedial Work***") required as a result of (a) any release or discharge of Hazardous Materials from the Premises, (b) any other contamination of the Premises caused by Hazardous Materials or (c) any violation of Hazardous Materials Laws caused by Tenant or any permitted assignee or subtenant of Tenant or their respective agents, contractors, employees, licensees or invitees, *except* in each case to the extent that any such release, discharge, contamination or violation was caused by Landlord or Landlord's Agents. Landlord shall have the right to intervene in any governmental action or proceeding involving any Remedial Work, and to approve performance of the work, in order to protect Landlord interests. Tenant shall be solely responsible for paying all fines, damages and penalties imposed by any Governmental Authority in connection with any Remedial Work pursuant to this Section 34.2.1.

34.2.2 Compliance with Insurance Requirements. During the Term, Tenant shall comply with the requirements of Tenant's insurers regarding Hazardous Materials and with such insurers' recommendations based upon prudent industry practices regarding management of Hazardous Materials.

34.2.3 Notice; Reporting. Tenant shall notify Landlord in writing immediately after any of the following: (a) Tenant has knowledge, or has reasonable cause to believe, that any Hazardous Material has been released or discharged under or about the Premises, whether or not the Hazardous Material is in quantities that would require reporting to a public agency; (b) Tenant receives any order of a Governmental Authority requiring any Remedial Work pursuant to any Hazardous Materials Laws; (c) Tenant receives any warning, notice of inspection, notice of violation or alleged violation, or Tenant receives notice or knowledge of any proceeding, investigation of enforcement action, pursuant to any Hazardous Materials Laws; or (d) Tenant receives written notice of any claims made by any third party against Tenant or the Premises relating to any loss or injury resulting from Hazardous Materials. Tenant shall deliver to Landlord copies of all test results, reports and business management plans required to be filed with any government agency pursuant to any Hazardous Materials Laws.

34.2.4 Entry and Inspection; Cure. Landlord and its agents, employees and contractors, shall have the right to enter the Premises at all reasonable times to inspect the Premises and Tenant's compliance with the terms and conditions of this Section 34, or to conduct investigations and tests. No prior notice to Tenant shall be required in the event of any emergency, or if Landlord has reasonable cause to believe that violations by Tenant of this

Section 34 have occurred, or if Tenant consents at the time of entry. In all other cases, Landlord shall give at least forty-eight (48) hours' prior written notice to Tenant. Landlord shall have the right, but not the obligation, to remedy any violation by Tenant of the provisions of this Section 34, or to perform any Remedial Work. Tenant shall pay, upon demand, all costs incurred by Landlord in remedying such violations or performing all Remedial Work, plus interest thereon at the rate of ten percent (10%) per annum from the date of demand until the date paid by the Tenant.

34.2.5 Termination/Expiration. Upon termination or expiration of this Lease, Tenant shall, at Tenant's cost, remove any equipment, improvements or storage facilities utilized in connection with any Hazardous Materials and shall clean up, detoxify, repair and otherwise restore the Premises to a condition in compliance with applicable laws governing Hazardous Materials. Upon termination or expiration of this Lease, Tenant shall permit Landlord, Landlord's Agents and Landlord's contractors and consultants to enter the Premises upon giving Tenant a twenty-four (24) hour written notice for the purposes of inspecting, at Tenant's cost, the environmental condition of the Premises, including an audit of any Hazardous Materials that are located on the Premises; provided, however, Landlord shall be responsible for the cost of such inspection in the event such inspection determines that the Premises are in material compliance with this Lease.

34.2.6 Indemnification. After the Term Commencement Date, Tenant shall indemnify, protect, defend and hold Landlord and Landlord's Agents harmless from and against any and all Claims arising after the Term Commencement Date and out of or in connection with (a) any breach of any provision of this Lease relating to the use, generation, storage, release,

disposal or transportation of Hazardous Materials by Tenant or any permitted assignee or subtenant, or their respective agents, contractors or employees upon the Premises (but not by Landlord or Landlord's Agents), on, under or about the Premises during the Term, or (b) contamination of the Premises by Hazardous Materials, in each case including, but not limited to, all foreseeable and unforeseeable consequential damages and the cost of any Remedial Work (even if resulting from Landlord's actual or passive negligence), but excepting any loss or injury to the extent resulting from the breach of the Lease by Landlord or the gross negligence or willful misconduct of Landlord, Landlord's Agents or Landlord's contractors or consultants. Neither the consent by Landlord to the use, generation, storage, release, disposal or transportation of Hazardous Materials, nor strict compliance with all Hazardous Materials Laws, shall excuse Tenant from Tenant's indemnification obligations pursuant to this Section 34.2.6. The foregoing indemnity shall be in addition to and not a limitation of the indemnification provisions of Section 9 of this Lease. Tenant's obligations pursuant to this Section 34.2.6 shall survive the termination or expiration of the Lease. The procedures set forth in Article 9 also will apply to this Section.

34.2.7 Default. The release or discharge of any Hazardous Material or violation of any Hazardous Materials Law by Tenant or any Tenant Agent shall be a material default by Tenant under the Lease, subject to the cure provisions set forth in Section 18.1.3. In addition to or in lieu of the remedies available under the Lease as a result of such default, Landlord shall have the right, without terminating the Lease, to require Tenant to suspend its operations and activities on the Premises until Landlord is satisfied that appropriate Remedial Work has been or is being adequately performed; Landlord's election of this remedy shall not constitute a waiver of Landlord's right thereafter to declare a default and pursue other remedies set forth in the Lease.

ARTICLE 35

Miscellaneous

35.1 Gender. Whenever the singular number is used in this Lease, the same shall include the plural, and the masculine gender shall include the feminine and neuter genders, and the word ***"person"*** shall include corporation, firm, or association, when required by the context.

35.2 Headings. The headings or title to the paragraphs of this Lease are for convenience only and do not in any way define, limit or construe the contents of such paragraphs.

35.3 Integration. This instrument contains all of the agreements and conditions made between the parties with respect to the hiring of the Premises and may not be modified orally or in any other manner other than by a written instrument signed by all the parties to this Lease.

35.4 Choice of Laws. The laws of the State of California as applied to contracts entered into between citizens of the State of California and to be performed within the State of California shall govern the validity, performance and enforcement of this Lease.

35.5 Severability. If any provision of this Lease is determined to be void by any court of competent jurisdiction, such determination shall not affect any other provisions of this Lease and such other provisions shall remain in full force and effect. If any provision of this Lease is capable of two constructions, one which would render the provision void and one which would render the provision valid, the provision shall be interpreted in the manner which would render it valid.

35.6 Amendment for Financing. Upon written request of Landlord, Tenant agrees to execute any lease amendments not materially altering the terms of this Lease, if required by the first mortgagee or beneficiary of a deed of trust encumbering real property of which the Premises constitute a part ("***Mortgagee***") incident to the financing of the real property of which the Premises constitute a part. Any change affecting the amount or timing of the consideration to be paid by Tenant or modifying the term of this Lease shall be deemed as materially alter the terms hereof.

35.7 Payments. Except as may otherwise be expressly stated, each payment required to be made by Tenant shall be in addition to and not in substitution for other payments to be made by Tenant.

35.8 Time of Essence. Time is of the essence in this Lease.

35.9 Force Majeure. For purposes of this Lease, "***Force Majeure***" shall mean any prevention, delay or stoppage due to strikes; lockouts; acts of God; acts of terrorism; adverse weather conditions; war; invasion; insurrection; acts of a public enemy; terrorism; riot; mob violence; civil commotion; sabotage; labor disputes; general shortage of labor, materials, facilities, equipment or supplies on the open market; delay in transportation; delays caused by new, or changes to existing, laws, rules, regulations or orders of any Governmental Authority; moratorium or other governmental action; inability to obtain

permits or approvals, including, without limitation, city and public utility approvals beyond the time periods that generally prevail for obtaining such permits and approvals; or any other cause beyond the reasonable control of Landlord and Landlord's Agents, financial ability excepted, whether similar or dissimilar to the foregoing. Any Force Majeure event shall excuse the performance by a party obligated to perform an obligation pursuant to this Lease (except for those obligations of Tenant to pay Rent pursuant to the terms of this Lease) for a period equal to the delay resulting from such Force Majeure event.

35.10 Notices and Communications. All notices or other communications to be given by one party to the other under this Lease shall be in writing, mailed or delivered to the other party at the following addresses:

Rent to Landlord:
BMR-GAZELLE COURT LLC
Attn: Accounting
17190 Bernardo Center Drive
San Diego, California 96128

Notices to Landlord:
BMR-GAZELLE COURT LLC
Attn: Vice President, Real Estate Counsel
17190 Bernardo Center Drive
San Diego, California 92128
Phone: (858) 485-9840 Fax: (858) 485-9843

With a copy to:
BMR-GAZELLE COURT LLC
Attn: Regional Director, West Coast Property Management
17190 Bernardo Center Drive
San Diego, California 92128
Phone: (858) 485-9840 Fax: (858) 485-9843

Notices to Tenant:
Isis Pharmaceuticals, Inc.
Attn: Chief Operating Officer
1896 Rutherford Road
Carlsbad, California 92008
Phone: (760) 931-9200 Fax: (760) 918-3599

with a copy to:
General Counsel
Fax: 760-268-4922

Notices may be delivered by Federal Express, United Parcel Service, or other nationally recognized overnight (one-night) mail courier service, or sent by facsimile (provided a copy of such notice is deposited with an overnight courier for next business day delivery). Any such notice shall be considered given on the date of such hand or couriered delivery, confirmed facsimile transmission if received on a business day, deposit with such overnight courier for next business day delivery.

Either party may, with proper notice, at any time designate a different address to which notices shall be sent.

35.11 Brokers.

35.11.1 Landlord and Tenant each represents to the other that it has had no dealings with any real estate broker or agent in connection with the negotiation and/or execution of this Lease other than CresaPartners ("***Broker***"), and that they know of no other real estate broker or agent that is or might be entitled to a commission in connection with this Lease. Tenant shall compensate Broker in relation to this Lease pursuant to a separate agreement between Tenant and Broker.

35.11.2 Tenant and Landlord represent and warrant that no broker or agent has made any representation or warranty relied upon by Tenant or Landlord in Tenant's or Landlord's decision to enter into this Lease, other than as contained in this Lease.

35.11.3 Tenant acknowledges and agrees that the employment of brokers by Landlord is for the purpose of solicitation of offers of leases from prospective tenants and that no authority is granted to any broker to furnish any representation (written or oral) or warranty from Landlord unless expressly contained within this Lease. Landlord and Tenant are executing this Lease in reliance upon each other's representations, warranties and agreements contained within Section 35.11.

35.11.4 Each of Landlord and Tenant agrees to indemnify, save, defend and hold the other harmless from any and all costs or liability for compensation claimed by any other broker or agent, other than Broker, employed or engaged by the indemnifying party or claiming to have been employed or engaged by the indemnifying party.

35.12 Confidentiality. During the course of this Lease the parties may exchange certain financial statements, accounting records and other documents that are clearly stamped "***confidential" ("Confidential Information***"). Landlord and Tenant hereby acknowledge and agree that the Confidential Information of each party is to be kept strictly confidential. Accordingly, except as may be required by law or court order, neither Landlord nor Tenant will, without the prior written consent of the other party, release, publish or otherwise distribute (and shall not authorize or permit any other person or entity to release, publish or otherwise distribute) any of the other party's Confidential Information to any person or entity other than such party's prospective lenders and purchasers of the Premises and legal and financial advisors, each of whom shall agree to hold such information strictly confidential as if such persons

were bound by the provisions of this Section 35.12. The obligations of this Section 35.12 will not apply to information that the receiving party can establish by written records (a) was known by it prior to the receipt of the confidential information from the disclosing party; (b) was disclosed to the receiving party by a third party having the right to do so; (c) was, or subsequently became, in the public domain through no fault of the receiving party, its officers, directors, employees or agents; or (d) was disclosed by the receiving party pursuant to any judicial, governmental or stock exchange request, requirement or order, so long as (to the extent permitted by Applicable Law) the receiving party provides the disclosing party with sufficient prior notice in order to allow the disclosing party to contest such request, requirement or order. Notwithstanding the foregoing, Landlord and Tenant may disclose on a confidential basis such information to such party's accountants, attorneys and other professional advisors in connection with the transactions contemplated by this Agreement.

35.13 Lease References. All exhibits and attachments to this Lease are incorporated by reference into this Lease, and all references in this Lease to the "***Lease***" shall mean the Lease inclusive of all exhibits and attachments thereto (including the Work Letter).

ARTICLE 36

OPTION TO EXTEND

36.1 Options To Extend. Tenant shall have the option to extend the term of this Lease for four (4) successive renewal periods of five (5) years each, subject to the following provisions:

36.1.1 Tenant shall have no right to exercise an option: (i) during the period commencing with the giving of any notice of default and continuing until said default is cured, (ii) during the period of time any Rent is unpaid, or (iii) in the event that Landlord has given three or more notices of separate monetary or material non-monetary breaches, whether or not the breaches are cured, during the twelve (12) months immediately preceding the exercise of the applicable option.

36.1.2 The period of time within which an option may be exercised shall not be extended or enlarged by reason of Tenant's inability to exercise an option because of the occurrence of one or more of the matters described in Section 36.1.1.

36.1.3 An option shall terminate and be of no further force or effect, notwithstanding Tenant's due and timely exercise of the option, if, after such exercise and prior to the commencement of the extended term, (i) Tenant fails to pay Rent for a period of thirty (30) days after such Rent becomes due, or (ii) an Event of Default occurs.

36.1.4 Tenant shall exercise an option by delivery of written notice to Landlord not less than twelve (12) months prior to the expiration of the Lease Term (as the same may have theretofor been extended by the exercise of a previous option pursuant to this Section 36). If said notice is not delivered within said time period, such option and all remaining options granted pursuant to this Section 36 shall automatically terminate and be of no further force or effect.

36.2 Rent During Option Periods.

36.2.1 Rent. The Base Monthly Rental payable by Tenant during any option period shall be the greater of: (a) 95% of the "***fair market rent"*** for the Premises at the commencement date of such option period, and (b) the Base Monthly Rental payable for the year immediately preceding the commencement date of such option period; provided, however, that the Base Monthly Rental payable during such option period shall be subject to the escalation provisions of Section 3.3 with the first such escalation occurring either (i) at the end of the second year of the extended term if the Base Monthly Rental is determined in accordance with Section 36.2.1(a) or (ii) upon the first day of the first Lease Year of the extended term if the Base Monthly Rental is determined in accordance with Section 36.2.1(b).

36.2.2 Fair Market Rent. For purposes if this Section 36.2.2, the "***fair market rent***" for the Premises shall be determined as of the date that is sixty (60) days prior to the first day of the first Lease Year of the extended term. If Landlord and Tenant cannot agree on the fair market rent of the Premises for any extension period by the sixtieth (60^{th}) day prior to the first day of the first Lease Year of the extended term, then, Landlord and Tenant shall each select, within fifteen (15) days of such sixtieth (60^{th}) day prior to the first day of the first Lease Year of the extended term, an appraiser who must be a qualified MAI appraiser with at least five (5) years experience appraising properties of similar type, use and location as the Premises to determine said "***fair market rent***." If one party fails to so designate an appraiser within the time required, the determination of "***fair market rent***" of the one appraiser who has been designated by the other party within the time required shall be binding on both parties. The appraisers shall submit their determinations of fair market rental value to both parties within fifteen (15) business days after their selection. If the difference between the two determinations is ten percent (10%) or less of the higher appraisal, then the average between the determinations shall be the fair market rental value of the Premises. If said difference is greater than ten percent (10%), then the two appraisers shall within fifteen (15) days of the date the second determination is submitted to

the parties designate a third appraiser who must also be a qualified MAI appraiser with at least five (5) years experience appraising properties of similar type, use and location as the Premises that is unaffiliated with either party hereto and that has not been retained or engaged by either party within the five (5) years preceding such appointment. If the two appraisers are unable to agree upon the selection of a third appraiser, then either Landlord or Tenant shall be entitled to apply to the presiding judge of the Superior Court of the County of San Diego, California for the selection of a third appraiser who shall be selected from a list of names of experienced appraisers submitted by Landlord or from a list of names submitted by Tenant, as the case may be, unless both Landlord and Tenant submit lists of names, in which case the Court, in its sole discretion, shall select the third appraiser from the lists. The sole responsibility of the third appraiser will be to determine which of the determinations made by the first two appraisers is most accurate. The third appraiser shall have no right to propose a middle ground or any modification of either of the determinations made by the first two appraisers. The third appraiser's choice shall be submitted to the parties within fifteen (15) business days after his or her selection. Such determination shall bind both of the parties and shall establish the fair market rental value of the Premises. Each party shall pay equal shares of the fees and expenses of the third appraiser. Fair market rent for the purposes of this Lease shall mean the then prevailing rent for buildings in the Carlsbad, California life science market, of comparable size, quality and location to the demised Premises, and leased on terms comparable to the terms contained in this Lease.

36.3 Intentionally Deleted.

36.4 Absolute Net Lease. After the Term Commencement Date, this Lease shall be deemed and construed to be an "absolute net lease" and the Landlord shall receive all payments required to be made by Tenant free from all charges, assessments, impositions, expenses, deductions of any and every kind or nature whatsoever. Landlord shall not be required to furnish any services or facilities or to make any repairs, replacements, or alterations of any kind in or on the Premises, except for the construction of the Building Improvements in accordance with this Lease. Tenant shall receive all invoices and bills relative to the Premises and, except as otherwise provided herein, shall pay for all expenses directly to the person or company submitting a bill without first having to forward payment for the expenses to Landlord. Tenant shall at Tenant's sole cost and expense be responsible for the management of the Premises, shall maintain the landscaping and parking lot, and shall make all additional repairs and alterations as required to maintain the Premises in first class condition.

36.5 Waiver of Jury Trial. To the extent permitted by Applicable Law, the parties hereby waive their respective rights to trial by jury in any action or proceeding brought by the other party and involving the Premises or arising out of this Lease. This Section is not intended to be, and shall not be interpreted to act as, a waiver to a trial by jury in any action by a party hereto against a third party.

36.6 Americans with Disabilities Act. Since compliance with the Americans with Disabilities Act (ADA) is dependent on Tenant's specific use of the Premises, Landlord makes no warranty or representation as to whether or not the Premises comply or will comply with the ADA or any similar legislation. Tenant shall cause the Building Improvements to be compliant with the ADA. In the event that Tenant's use of the Premises requires modifications or additions to the Premises in order to be in ADA compliance, Tenant agrees to make any such necessary modifications and/or additions at Tenant's expense.

36.7 Tenant's Authority. Tenant hereby represents, warrants and covenants that (a) Tenant is duly incorporated or otherwise established or formed and validly existing under the laws of its state of incorporation, establishment or formation, (b) Tenant has and is duly qualified to do business in the state in which the Premises is located, (c) Tenant has full corporate, partnership, trust, association or other appropriate power and authority to enter into this Lease and to perform all Tenant's obligations hereunder and (d) each person (and all of the persons if more than one signs) signing this Lease on behalf of Tenant is duly and validly authorized to do so.

36.8 Landlord's Authority. Landlord hereby represents, warrants and covenants that (a) Landlord is duly incorporated or otherwise established or formed and validly existing under the laws of its state of incorporation, establishment or formation, (b) Landlord has and is duly qualified to do business in the state in which the Property is located, (c) Landlord has full corporate, partnership, trust, association or other appropriate power and authority to enter into this Lease and to perform all Landlord's obligations hereunder and (d) each person (and all of the persons if more than one signs) signing this Lease on behalf of Landlord is duly and validly authorized to do so.

[Signature Page Follows]

IN WITNESS WHEREOF, Landlord and Tenant have executed this Lease as of the Effective Date.

LANDLORD:

BMR-GAZELLE COURT LLC,
a Delaware limited liability company

By: /s/ John Bonanno
Name: John Bonanno
Title: Vice President, Development

TENANT:

ISIS PHARMACEUTICALS, INC.,
a Delaware corporation

By: /s/ B. Lynne Parshall
Name: B. Lynne Parshall
Title: Chief Operating Officer & Chief Financial Officer

[ISIS GAZELLE COURT LEASE SIGNATURE PAGE]

APPENDIX A

DEFINED TERMS

DEFINED TERM	SECTION REFERENCE
89% Cap	Section 3.1.2
Accelerated Purchase Option Closing Date	Section 19.1.4
Act of Bankruptcy	Section 18.1.7
Additional Rent	Section 3.4
Aggregate Disbursements	Section 1.4
Annual Statement	Section 10.2
Applicable Laws	Section 5.2
Approved Design Development Plans	Work Letter Section 2.1
Approved Plans	Section 3.3
Approved Shell and Core Plans	Section 2.2
Work Letter Approved TI Plans	Section 3.3

Architect	Work Letter Section 1.2
Architect's Agreement	Work Letter Section 7
Association	Section 32.4
Associations	Section 32.2
Base Monthly Rental	Section 3.1.1
Base Monthly Rent Commencement Date	Section 3.1.1
Broker	Section 35.11.1
Budget	Work Letter Section 6.1
Building	Recitals
Building Improvements	Section 1.2.3
CC&Rs	Section 5.4
Claims	Section 4.3.3
CPI	Section 24.2.4
CPI Adjustment Factor	Section 24.2.4
Complete	Work Letter Section 8
Confidential	Section 35.12
Confidential Information	Section 35.12
Construction Agreements	Work Letter Section 7
Construction Allowance	Section 1.4
Construction Allowance Costs	Section 1.4
Damage Determination Notice	Section 20.6
Default Rate	Section 3.5
Design Development TI Plans	Work Letter Section 3.1
Design Problem	Section 2.4(a)(ii)
Disbursement	Work Letter Section 6.2
Disbursement Request	Work Letter Section 6.2
Early Entry Event	Section 4.3.1
Effective Date	Preamble
Entitlements	Section 1.2.1

Estimated Substantial Completion Date	Section 1.3.2
Event of Default	Section 18.1
Exempt Assignment	Section 16.3
Exempt Sublease	Section 16.1.2
Exit Survey	Section 7.1.3
Fair Market Rent	Section 36.2.1
Fair Market Value	Section 24.2.5(b)
Fire and Extended Coverage	Section 10.3.2
Firm Completion Date	Section 19.3.2
Force Majeure	Section 35.9
General Contractor	Work Letter Section 1.2
GMP Contract	Work Letter Section 1.3
Governmental Authority	Section 5.2
Hazardous Materials	Section 34.1.2
Hazardous Materials Laws	Section 34.1.1
Improvements	Section 1.1
Indemnifying Party	Section 9.4
Indemnitee	Section 9.4
Insurance Costs	Section 10.2
Land	Recitals
Landlord	Preamble
Landlord's Agents	Section 9.1.1
Landlord's Authorized Representative	Work Letter Section 1.1(a)
Landlord's Construction Work	Section 1.2.3
Landlord's Construction Work Plans	Work Letter Section 2.2
Landlord's Entitlement Termination Right	Section 19.2.1
Lease	Section 35.13
Lease Term	Section 2.2
Lease Year	Section 24.2
LIBOR	Section 1.4
Material Contractor	Work Letter Section 1.2
Memorandum of Lease	Section 27.3
Mortgagee	Section 35.6
Offer Period	Section 24.3
Parties	Preamble
Pending Disbursements	Section 3.1.1
Permitted Sublease	Section 16.1.2
Permitted Use	Section 5.1
Person	Section 35.1
PO Model	Section 24.2.5(a)
Premises	Section 20.1
Punchlist Items	Section 1.2.3
Punchlist Sign-off Date	Section 3.1.1

Purchase and Sale Agreement	Section 24.2.4
Purchase Option	Section 24.2.1

Purchase Option Closing Date	Section 24.2.1
Purchase Option Exercise Notice	Section 24.2.3
Real Estate Taxes	Section 12.3
Remedial Work	Section 34.2.1
Rent	Section 3.4
Base Monthly Rent Commencement Date	Section 3.1.1
Rules and Regulations	Section 5.4
Sale Notice	Section 24.3
SEC	Section 26.3
Security Deposit	Section 3.6.1
Security Deposit Trigger Event	Section 3.6.1
Shell and Core Change	Work Letter Section 2.4
Shell and Core Landlord Change Order Request	Work Letter Section 2.4(b)(i)
Shell and Core Permitted Change	Work Letter Section 2.4(c)
Shell and Core Tenant Change Order Request	Work Letter Section 2.4(a)(i)
Significant Subcontractors and Material Suppliers	Work Letter Section 1.2
Substantial Completion	Section 1.2.4
Substantially Complete	Section 1.3.2
Techbilt	Section 1.3
Techbilt PSA	Section 19.2.2
Techbilt Repurchase Option	Section 19.2.2
Techbilt Termination Event	Section 19.2.2
Tenant	Preamble
Tenant Affiliate	Section 16.1.2
Tenant Alterations	Section 6.2
Tenant Alterations Allowance	Section 6.2
Tenant Delay	Section 19.3.2
Tenant Improvements	Section 1.3.1
Tenant Requested Disbursement	Work Letter Section 6.2
Tenant’s Acceptance Notice	Section 24.3
Tenant’s Agents	Section 4.3.3
Tenant’s Authorized Representative	Work Letter Section 1.1(b)
Term Commencement Date	Section 2.2
Term Expiration Date	Section 2.2
Third Party Beneficiary Warranty	Work Letter Section 1.2
TI Change	Work Letter Section 3.3
TI Landlord Change Order Request	Work Letter Section 3.3(b)(i)
TI Permitted Change	Work Letter Section 3.3(c)
TI Plans	Work Letter Section 3.2
TI Tenant Change Order Request	Work Letter Section 3.3(a)(i)
Transfer Notice	Section 16.2
Warranty Issue	Work Letter Section 1.2
Work Letter	Section 1.2.3
Worth at the Time of Award	Section 19.1.3.1

EXHIBIT A

DESCRIPTION OF THE LAND

PARCEL 1:

PARCEL “A” OF CERTIFICATE OF COMPLIANCE NO. ADJ 09-05 RECORDED JANUARY 19, 2010 AS INSTRUMENT NO. 2010-0024854 OF OFFICIAL RECORDS, DESCRIBED AS FOLLOWS:

LOT 14 OF CARLSBAD TRACT NO. 97-13-02, ACCORDING TO MAP THEREOF NO. 15505, IN THE CITY OF CARLSBAD, COUNTY OF SAN DIEGO, STATE OF CALIFORNIA, RECORDED IN THE OFFICE OF THE COUNTY RECORDER OF SAN DIEGO COUNTY ON JANUARY 23, 2007 AS FILE NO. 2007-0047588, TOGETHER WITH A PORTION OF LOT ‘B’ OF RANCHO AGUA HEDIONDA, IN THE CITY OF CARLSBAD, COUNTY OF SAN DIEGO, STATE OF CALIFORNIA, ACCORDING TO MAP THEREOF NO. 823, FILED IN THE OFFICE OF THE COUNTY RECORDER OF SAN DIEGO COUNTY, NOVEMBER 16, 1896, BEING MORE PARTICULARLY DESCRIBED AS FOLLOWS:

BEGINNING AT THE NORTHWEST CORNER OF SAID LOT 14; THENCE, ALONG THE NORTH LINE OF SAID LOT 14, NORTH 89°09’41” EAST 629.31 FEET; THENCE SOUTH 00°31’59” WEST 8.11 FEET; THENCE NORTH 89°53’58” EAST 392.46 FEET; THENCE NORTH 53°13’30” EAST 15.15 FEET; THENCE SOUTH 56°49’30” EAST 85.95 FEET TO THE NORTHEAST CORNER OF SAID LOT 14, SAID CORNER BEING ON A NON-TANGENT 264.00 FOOT RADIUS CURVE CONCAVE NORTHWESTERLY, THE RADIAL LINE TO SAID POINT BEARS SOUTH 56°49’30” EAST; THENCE, ALONG THE EAST LINE OF SAID LOT 14, SOUTHWESTERLY ALONG SAID CURVE THROUGH A CENTRAL ANGLE OF 5°50’08” AN ARC DISTANCE OF DISTANCE OF 26.89; THENCE, TANGENT TO SAID CURVE, SOUTH 39°00’38” WEST 329.54 FEET TO THE BEGINNING OF A TANGENT 736.00 FOOT RADIUS CURVE CONCAVE SOUTHEASTERLY; THENCE SOUTHWESTERLY ALONG SAID CURVE THROUGH A

CENTRAL ANGLE OF 25°07’33” A DISTANCE OF 322.76 TO THE SOUTHEAST CORNER OF SAID LOT 14, SAID CORNER ALSO BEING A POINT ON THE SUBDIVISION BOUNDARY OF MAP NO. 14926; THENCE, ALONG THE SOUTH LINE OF SAID LOT 14 AND THE BOUNDARY OF SAID MAP NO. 14926, NON-TANGENT TO SAID CURVE NORTH 52°33’23” WEST 148.70 FEET; THENCE SOUTH 48°06’30” WEST, 21.89 FEET TO THE BEGINNING OF A 100.00 FOOT RADIUS CURVE CONCAVE NORTHWESTERLY; THENCE SOUTHWESTERLY ALONG SAID CURVE THROUGH A CENTRAL ANGLE OF 34°22’48” AN ARC DISTANCE OF 60.00 FEET; THENCE 82°29’18” WEST 147.20 FEET; THENCE NORTH 89°14’55” WEST 410.06 FEET TO THE SOUTHWEST CORNER OF SAID LOT 14; THENCE, LEAVING SAID LOT 14 AND CONTINUING ALONG THE BOUNDARY OF SAID MAP NO. 14926, SOUTH 29°36’38” WEST 51.14 FEET; THENCE NORTH 77°38’20” WEST 216.59 FEET; THENCE, LEAVING THE BOUNDARY OF SAID MAP NO. 14926, NORTH 43°05’58” EAST 78.45 FEET; THENCE NORTH 01°47’45” EAST 442.55 FEET TO A POINT ON THE SOUTHERLY BOUNDARY OF THAT PUBLIC STREET AND UTILITY EASEMENT RECORDED JANUARY 23, 2007 AS FILE NO. 2007-0047586, SAID POINT BEING ON A NON-TANGENT 836.00 FOOT RADIUS CURVE CONCAVE NORTHERLY, A RADIAL LINE TO SAID POINT BEARS SOUTH 23°00’29” WEST; THENCE, EASTERLY ALONG SAID EASEMENT AND SAID CURVE, THROUGH A CENTRAL ANGLE OF 10°54’11” AN ARC DISTANCE OF 159.09 TO THE BEGINNING OF A COMPOUND 56.00 FOOT RADIUS CURVE CONCAVE WESTERLY; THENCE NORTHERLY ALONG SAID CURVE THROUGH A CENTRAL ANGLE OF 181°26’49” AN ARC DISTANCE OF 177.34 TO THE POINT OF BEGINNING.

PARCEL 2:

AN EASEMENT FOR A PRIVATE DRAINAGE OVER AND ACROSS LOT 4 OF CARLSBAD TRACT NO. 97-13-01, CARLSBAD OAKS NORTH PHASE 1, IN THE CITY OF CARLSBAD, COUNTY OF SAN DIEGO, STATE OF CALIFORNIA, ACCORDING TO MAP THEREOF NO. 14926, RECORDED IN THE OFFICE OF THE COUNTY RECORDER OF SAN DIEGO COUNTY ON DECEMBER 15, 2004, AS CREATED BY EASEMENT AGREEMENT EXECUTED BY KILROY REALTY FINANCE PARTNERSHIP, L.P., A DELAWARE LIMITED PARTNERSHIP, TECHBILT CONSTRUCTION CORP., A CALIFORNIA CORPORATION AND CARLSBAD OAKS NORTH PARTNERS, L.P., A CALIFORNIA LIMITED PARTNERSHIP, DATED JANUARY 20, 2010 AND RECORDED JANUARY 29, 2010 AS INSTRUMENT NO. 2010-0047608 OF OFFICIAL RECORDS.

APN: 209-120-11 and a portion of 209-120-17

EXHIBIT B

WORK LETTER

This Work Letter (this “***Work Letter***”) is made and entered into as of the Effective Date, by and between Landlord and Tenant, and is attached to and made a part of that certain Lease dated as of the Effective Date (as the same may be amended, restated, supplemented or otherwise modified from time to time, the “***Lease***”), by and between Landlord and Tenant for the Premises. All capitalized terms used but not otherwise defined herein shall have the meanings ascribed thereto in the Lease.

1. General Requirements.

1.1. Authorized Representatives.

(a) Landlord designates, as Landlord’s authorized representative (“***Landlord’s Authorized Representative***”), (i) Federico Mina as the person authorized to initial plans, drawings, and approvals pursuant to this Work Letter and (ii) John Bonanno as the person authorized to initial plans, drawings, and approvals and to sign change orders pursuant to this Work Letter and any amendments to this Work Letter or the Lease. Tenant shall not be obligated to respond to or act upon any such item until such item has been initialed or signed (as applicable) by the appropriate Landlord’s Authorized Representative. Landlord may change Landlord’s Authorized Representative upon one (1) business day’s prior written notice to Tenant.

(b) Tenant designates B. Lynne Parshall (“***Tenant’s Authorized Representative***”) as the person authorized to initial all plans, drawings, change orders and approvals pursuant to this Work Letter. Landlord shall not be obligated to respond to or act upon any such item until such item has been initialed or signed (as applicable) by Tenant’s Authorized Representative. Tenant may change Tenant’s Authorized Representative upon one (1) business day’s prior written notice to Landlord.

1.2. Landlord’s Architects, Contractors and Consultants. The architect, engineering consultants, design team, general contractor and major subcontractors responsible for the construction of the Building Improvements shall be selected by Landlord and approved by Tenant, which approval Tenant shall not unreasonably withhold, condition or delay. Tenant may refuse to use any architects, consultants, contractors, subcontractors or material suppliers that Tenant reasonably believes could cause labor disharmony. The “***Architect***” shall be DG Architects, Inc. dba DGA (or such other architect as may be proposed by Landlord and approved by Tenant in writing, such approval not to be unreasonably withheld, conditioned or delayed). The “***Project Manager***” shall be Project Management Advisors, Inc. dba PMA (or such other project manager as may be proposed by Landlord and approved by Tenant in writing, such approval not to be unreasonably withheld, conditioned or delayed). The “***General Contractor***” shall be DPR, Inc. (or such other general contractor as may be proposed by Landlord and approved by Tenant in writing, such approval not to be unreasonably withheld, conditioned or delayed). As used in this Work Letter, “***significant subcontractors and material suppliers***” means those subcontractors and suppliers which have been, or will be, paid at least One Million

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Dollars ($1,000,000) in connection with the work and materials provided by such party in connection with the Building Improvements. Landlord shall endeavor to cause Tenant to be designated as a third party beneficiary with respect to each warranty and/or indemnity with respect to the Landlord’s Construction Work that is made by any “significant subcontractors and material suppliers” against which Landlord is able to exercise remedies pursuant to a contractual right (each, a ***“Material Contractor”***, and each such warranty/indemnity, a ***“Third Party Beneficiary Warranty”***); *provided*, *however*, that Tenant shall not exercise its rights with respect to any Third Party Beneficiary Warranty unless (a) Tenant identifies any part of the Landlord’s Construction Work that violates such Third Party Beneficiary Warranty (a ***“Warranty Issue”***), (b) Tenant provides Landlord with written notice of any Warranty Issue, (c) the GMP Contract does not prohibit Landlord as the owner or Tenant as the third party beneficiary from exercising its rights with respect to such warranty/indemnity, and (d) either (i) within fifteen (15) business days after receiving such notice from Tenant, Landlord has not requested that the respective Material Contractor address such Warranty Issue, or (ii) Landlord fails to diligently endeavor to cause the Material Contractor to address such Warranty Issue.

1.3. GMP Contract. Landlord covenants that it will use commercially reasonable efforts to, within one-hundred fifty (150) days following the Effective Date, enter into a guaranteed maximum price contract between Landlord and General Contractor which shall provide for the one hundred percent (100%) lien-free completion of the Building Improvements, in accordance with the Budget (the "***GMP Contract***"). The GMP Contract shall be in form and substance reasonably acceptable to Tenant and contain a complete line item budget to complete the Building Improvements. Tenant shall be a named indemnified party with respect to any indemnities provided by the General Contractor under the GMP Contract, and shall be a third party beneficiary with respect to each warranty and indemnity made by the General Contractor under the GMP Contract.

1.4. Schedule. The schedule for the design, development, and completion of the Building Improvements is attached hereto as Schedule 1 to the Work Letter (the ***"Schedule"***). The Schedule is for informational purposes only and is not binding on Landlord in any respect, provided that the provisions of this Section 1.4 shall not limit Tenant's rights under Section 19.3.2 or Section 19.3.4 of the Lease. Landlord will use commercially reasonable efforts to provide Tenant with updates to the Schedule; *provided* at a minimum, within ten (10) days of Landlord's receipt of a written request from Tenant, Landlord shall provide Tenant with an updated Schedule and a reconciliation of the actual progress of Landlord's Construction Work against the Schedule.

2. Shell and Core. Landlord's Construction Work related to the Shell and Core shall be performed by Landlord at Landlord's sole cost and expense substantially in accordance with the Approved Shell and Core Plans, subject only to changes made in accordance with Section 2.4.

2.1. Approved Design Development Plans. Landlord has approved those certain design development plans submitted by Tenant and more particularly described on Schedule 2 to the Work Letter (the "***Approved Design Development Plans***").

2.2. Approved Shell and Core Plans. Landlord shall cause the Architect to prepare final plans and specifications for the Shell and Core that (a) are consistent with and are logical evolutions of the Approved Design Development Plans and (b) incorporate any Shell and Core Permitted Changes, and (c) incorporate any other Landlord-requested (and Tenant approved) Shell and Core Changes. As soon as such final plans and specifications ("***Landlord's Shell and Core Plans***") are completed, Landlord shall deliver the same to Tenant for Tenant's approval, which approval may be reasonably withheld only if: (i) the Landlord's Shell and Core Work Plans are neither consistent with nor logical evolutions of the Approved Design Development Plans, (ii) Tenant requests changes to the Landlord's Shell and Core Plans in accordance with Section 2.4(a), or (iii) Tenant objects to any Landlord requested Shell and Core Change (other than Shell and Core Permitted Changes). Such Landlord's Shell and Core Plans shall be approved or disapproved by Tenant within ten (10) business days after delivery to Tenant. If Tenant fails to respond within such ten (10) business day period, Landlord shall provide a written reminder notice to Tenant. Tenant's failure to respond to such reminder notice within five (5) business days after delivery of such notice shall be deemed approval by Tenant of the Landlord's Shell and Core Plans. If the Landlord's Shell and Core Plans are disapproved by Tenant, then Tenant shall notify Landlord in writing of its detailed objections to such Landlord's Shell and Core Plans and shall submit any Shell and Core Changes through a Shell and Core Tenant Change Order Request, and the parties shall confer and then negotiate in good faith to reach agreement on the Landlord's Shell and Core Plans. After the Landlord's Shell and Core Plans are approved by Landlord and Tenant, two (2) copies of such Landlord's Shell and Core Plans shall be initialed and dated by Landlord and Tenant, and Landlord shall promptly submit such Landlord's Shell and Core Plans to each appropriate Governmental Authority for approval. The Landlord's Shell and Core Plans so approved, and all change orders and other changes thereto specifically permitted by this Work Letter, are referred to herein as the "***Approved Shell and Core Plans***."

2.3. [***] Fee. Tenant shall [***] Landlord a [***] fee.

2.4. Changes to Shell and Core Plans. Any changes to the Landlord's Shell and Core Plans or the Approved Shell and Core Plans (each, a "***Shell and Core Change"***) requested by Landlord or Tenant (other than Shell and Core Permitted Changes by Landlord which do not require any approval) shall be requested and instituted in accordance with the provisions of this Section 2.4 and shall be subject to the written approval of the other party in accordance with this Work Letter.

(a) Shell and Core Changes Requested by Tenant.

(i) Shell and Core Tenant Change Order Request. Tenant may request Shell and Core Changes to the Landlord's Construction Work Plans or the Approved Shell and Core Plans by notifying Landlord thereof in writing in substantially the same form as the AIA standard change order form (a "***Shell and Core Tenant Change Order Request***"), which Shell and Core Tenant Change Order Request shall detail the nature and extent of any requested Shell and Core Changes, including, without limitation, (A) the Shell and Core Change and (B) any modification of the Landlord's Construction Work Plans or the Approved Shell and Core Plans, as applicable. In the event Landlord approves any Shell and Core Change, Landlord shall: (1) notify Tenant if it reasonably believes such Shell and Core Change could cause a delay in the Estimated Substantial Completion Date; and (2) provide Landlord's reasonable estimate of any additional costs and expenses associated with such Shell and Core Change. Shell and Core Tenant Change Order Requests shall be signed by Tenant's Authorized Representative.

(ii) Landlord's Approval of Shell and Core Changes. All Tenant-requested Shell and Core Changes shall be subject to Landlord's prior written approval, which shall not be unreasonably withheld, conditioned or delayed so long as such Shell and Core Change, as reasonably determined by Landlord, (A) could not reasonably be expected to (1) adversely impact (a) the exterior appearance of the Building, (b) the structural aspects of the Building, (c) Landlord's ability to construct Landlord's Construction Work or Tenant's ability to operate its business in the Building (d) any building system, including, without limitation, the HVAC, mechanical, electrical, plumbing or life safety systems installed in connection with the Landlord's Construction Work; (2) create a foreseeable risk of violating any Applicable Law or permit requirement or materially increasing insurance premiums; (3) violate any recorded document affecting the Property; (4) cause the Building to be inconsistent with the quality and scope of a class "A" office buildings in the vicinity of the Building; (5) involve a use of the Premises that is inconsistent with the Permitted Use; (6) extend the Estimated Substantial Completion Date beyond fifteen (15) days (such 15-day extension to apply separately to each Shell and Core Tenant Chang Order Request), nor (7) in Landlord's reasonable judgment, reduce the quality or value of the Building or the Property (each, a "***Design Problem***"), and (B) will not cause the Aggregate Disbursements to exceed the total amount set forth in the Budget. Landlord shall have ten (10) days after receipt of a Shell and Core Tenant Change Order Request to notify Tenant in writing of Landlord's decision either to proceed with or abandon Tenant-requested Shell and Core Change. If Landlord does not approve in writing a Tenant requested Shell and Core Change within ten (10) days after receipt of a Shell and Core Tenant Change Order Request, then such Shell and Core Tenant Change Order Request shall be deemed rejected by Landlord, and Landlord's Construction Work shall not be altered as contemplated

by such Shell and Core Tenant Change Order Request. If Landlord disapproves the Shell and Core Tenant Change Order Request, then the parties shall confer and negotiate in good faith to reach agreement on the Shell and Core Tenant Change Order Request.

(b) Shell and Core Changes Requested by Landlord.

(i) Shell and Core Landlord Change Order Request. Landlord may request Shell and Core Changes to Landlord's Construction Work by notifying Tenant thereof in writing in substantially the same form as the AIA standard change order form (a "***Shell and Core Landlord Change Order Request***"), which Shell and Core Landlord Change Order Request shall detail the nature and extent of any requested Shell and Core Changes, including, without limitation, (A) the Shell and Core Change, (B) any modification of the Landlord's Construction Work Plans or the Approved Shell and Core Plans, as applicable, and (C) any changes to the Estimated Substantial Completion Date resulting from the Shell and Core Change.

(ii) Tenant's Approval of Shell and Core Change. Tenant shall have ten (10) days after receipt of a Shell and Core Landlord Change Order Request to notify Landlord in writing of Tenant's approval or rejection of the Landlord-requested Shell and Core Change, which approval shall not be unreasonably withheld, conditioned or delayed. If Tenant fails to respond within such ten (10) day period, then Landlord shall provide Tenant with a second written notice stating that "Tenant's failure to respond within three (3) days after Landlord's second notice shall be deemed Tenant's approval to such Shell and Core Landlord Change Order Request," and if Tenant does not respond within such three (3) day period, then Tenant shall be deemed to have approved such Shell and Core Landlord Change Order Request.

(c) Shell and Core Permitted Changes. For purposes of this Work Letter, a "***Shell and Core Permitted Change***" shall mean: (i) minor field changes; (ii) changes required by Governmental Authority; (iii) any other changes that: (A) do not cause a Design Problem, and (B) do not materially change the size, cost, configuration, or overall appearance of the Building or Landlord's ability to construct Landlord's Construction Work or Tenant's ability to operate its business in the Building, and (iv) changes required for the ordinary development of the Approved Shell and Core Plans in a manner not inconsistent with the Approved Shell and Core Plans. Shell and Core Permitted Changes may be made by Landlord in its sole discretion without Tenant's consent.

3. Tenant Improvements. The Tenant Improvements shall be performed by Landlord at Landlord's sole cost and expense substantially in accordance with the Approved TI Plans, subject only to changes made in accordance with Section 3.3.

3.1 Design Development TI Plans. Landlord has approved those certain design development plans submitted by Tenant and more particularly described on Schedule 3 to the Work Letter (the "***Design Development TI Plans***").

3.2. Approved TI Plans. Landlord shall prepare final plans and specifications for the Tenant Improvements that: (a) are consistent with and are logical evolutions of the Design Development TI Plans, (b) incorporate any TI Permitted Changes, and (c) incorporate any other Landlord-requested (and Tenant approved) TI Changes. As soon as such final plans and specifications ("***TI Plans***") are completed, Landlord shall deliver the same to Tenant for Tenant's approval, which approval may be reasonably withheld only if: (i) the TI Plans are neither consistent with nor logical evolutions of the Design Development TI Plans, (ii) Tenant intends to request changes to the TI Plans in accordance with Section 3.3(a)(i), or (iii) Tenant objects to any Landlord requested TI Change (other than TI Permitted Changes). Such TI Plans shall be approved or disapproved by Tenant within ten (10) business days after delivery to Tenant. If Tenant fails to notify Landlord of disapproval within such ten (10) day period, then Landlord shall provide Tenant with a second written notice stating that "Tenant's failure to respond within five (5) days after Landlord's second notice shall be deemed Tenant's approval to such TI Plans," and if Tenant does not respond within such five (5) day period, then Tenant shall be deemed to have approved such TI Plans. If the TI Plans are disapproved by Tenant, Tenant shall notify Landlord in writing of its objections to such TI Plans and shall submit any requested TI Changes through a TI Tenant Change Order Request, and then the parties shall confer and negotiate in good faith to reach agreement on the TI Plans. After the TI Plans are approved by Landlord and Tenant, two (2) copies of such TI Plans shall be initialed and dated by Landlord and Tenant as soon as approved by Landlord and Tenant, and Landlord shall promptly submit such TI Plans to each appropriate Governmental Agency for approval. The TI Plans so approved, and all change orders and other changes thereto specifically permitted by this Work Letter, are referred to herein as the "***Approved TI Plans***" and shall become part of the Lease as though set forth in full. The Approved Shell and Core Plans together with the Approved TI Plans shall be referred to herein and in the Lease as the "***Approved Plans***."

3.3. Changes to Tenant Improvements. Any changes to the TI Plans or the Approved TI Plans (each, a "***TI Change***") requested by Landlord or Tenant (other than TI Permitted Changes by Landlord which do not require any approval) shall be requested and instituted in accordance with the provisions of this Section 3.3 and shall be subject to the written approval of the other party in accordance with this Work Letter.

(a) TI Changes Requested by Tenant.

(i) TI Tenant Change Order Request. Tenant may request TI Changes after Tenant approves the Design Development TI Plans or the Approved TI Plans, as applicable, by notifying Landlord thereof in writing in substantially the same form as the AIA standard change order form (a "***TI Tenant Change Order Request***"), which TI Tenant Change Order Request shall detail the nature and extent of any requested TI Changes, including, without limitation, (A) the TI Change and (B) any modification of the TI Plans or the Approved TI Plans, as applicable. In the event Landlord approves such TI Change, Landlord shall: (1) notify Tenant if it reasonably believes such TI Change could cause a delay in the Estimated Substantial Completion Date; and (2) provide Landlord's reasonable estimate of any additional costs and expenses associated with such TI Change.

(ii) Landlord's Approval of TI Changes. All Tenant-requested TI Changes shall be subject to Landlord's prior written approval, which shall not be unreasonably withheld, conditioned or delayed so long as such TI Change (A) would not create a Design Problem, (B) will not cause the Aggregate Disbursements to exceed the total amount set forth in the Budget. Landlord shall have ten (10) days after receipt of a TI Tenant Change Order Request to notify Tenant in writing of Landlord's decision either to proceed with or abandon Tenant-requested TI Change. If Landlord does not approve in writing a Tenant requested TI Change within ten (10) days after receipt of a TI Tenant Change Order Request, then such TI Tenant Change Order Request shall be deemed rejected by Landlord, and the Tenant Improvements shall not be altered as contemplated by such TI Tenant Change Order Request. If Landlord disapproves the TI Tenant Change Order Request, then the parties shall confer and negotiate in good faith to reach agreement on the TI Tenant Change Order Request.

(b) TI Changes Requested by Landlord.

(i) TI Landlord Change Order Request. Landlord may request TI Changes by notifying Tenant thereof in writing in substantially the same form as the AIA standard change order form (a "***TI Landlord Change Order Request***"), which TI Landlord Change Order Request shall detail the nature and extent of any requested TI Changes, including, without limitation, (A) the TI Change, (B) any modification of the TI Plans or the Approved TI Plans, as applicable, and (C) any changes to the Estimated Substantial Completion Date resulting from the TI Change.

(ii) Tenant's Approval of TI Change. Tenant shall have ten (10) days after receipt of a TI Landlord Change Order Request to notify Landlord in writing of Tenant's approval or rejection of the Landlord-requested TI Change, which approval shall not be unreasonably withheld, conditioned or delayed. If Tenant fails to respond within such ten (10) days period, then Landlord shall provide Tenant with a second written notice stating "that Tenant's failure to respond within three (3) days after Landlord's second notice shall be deemed Tenant's approval to such Landlord-requested TI Change," and if Tenant does not respond within such three (3) day period, then Tenant shall be deemed to have approved such Landlord-requested TI Change.

(c) TI Permitted Changes. For purposes of this Work Letter, a "***TI Permitted Change***" shall mean: (i) minor field changes; (ii) changes required by Governmental Authority; (iii) any other changes that: (A) do not cause a Design Problem, and (B) do not materially change the size, cost, configuration, or overall appearance of the Tenant Improvements or Tenant's ability to operate its business in the Building; and (iv) ordinary development of the Approved TI Plans in a manner not inconsistent with the Approved TI Plans. TI Permitted Changes may be made by Landlord in its sole discretion without Tenant's consent.

4. Insurance.

4.1. Property Insurance. At all times during the period beginning with commencement of construction of the Building Improvements and ending when the Building Improvements are deemed Complete pursuant to Section 8 of this Work Letter, Landlord shall maintain or cause to be maintained (in addition to the insurance required pursuant to the Lease) property insurance insuring Landlord and its affiliates, agents and employees, as their interests may appear. Such policy shall, on a completed values basis for the full insurable value at all times, insure against loss or damage by fire, vandalism and malicious mischief and other such risks as are customarily covered by the so-called "broad form extended coverage endorsement" upon all Building Improvements and the General Contractor's and any subcontractors' machinery, tools and equipment, all while each forms a part of, or is contained in, the Tenant Improvements or any temporary structures on the Premises, or is adjacent thereto; provided that, for the avoidance of doubt, insurance coverage with respect to the General Contractor's and any subcontractors' machinery, tools and equipment shall be carried on a primary basis by such General Contractor or subcontractor. Landlord agrees to pay any deductible, which deductible amount shall be considered a Disbursement pursuant to the terms of the Lease. Said property insurance shall contain an express waiver of any right of subrogation by the insurer against Tenant and its affiliates, agents and employees, and shall name Tenant and its affiliates as loss payees as their interests may appear.

4.2 Workers' Compensation Insurance. At all times during the period of construction of the Building Improvements, Landlord shall, and shall cause its contractors or subcontractors to, maintain statutory workers' compensation insurance as required by Applicable Laws.

5. Requests for Consent. Except as otherwise provided in this Work Letter, Tenant shall respond to all requests for consents, approvals or directions made by Landlord pursuant to this Work Letter within ten (10) days following Tenant's receipt of such request. If Tenant fails to respond within such ten (10) days period, then Landlord shall provide Tenant with a second written notice stating that "Tenant's failure to respond within three (3) days after Landlord's second notice shall be deemed approval by Tenant," and if Tenant does not respond within such three (3) day period, then Tenant shall be deemed to have approved such item.

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6. Construction Allowance.

6.1. Budget; Disbursements. A budget for all hard and soft costs pertaining to the Building Improvements is attached hereto as Schedule 4 to the Work Letter (as the same may be modified in accordance with this Work Letter, the "***Budget***"). Landlord may reallocate line items within the Budget in its sole discretion at any time. Landlord will use commercially reasonable efforts to provide Tenant with updates to the Budget; *provided* at a minimum, within ten (10) days of Landlord's receipt of a written request from Tenant, Landlord shall provide Tenant with an updated Budget and a reconciliation of actual costs incurred through the date that is sixty days prior to the date of Tenant's written request to the Budget. In addition, Landlord will (or will request that the Project Manager) copy Isis' Chief Accounting Officer on all draw packages submitted to Landlord by the Project Manager related to the Building Improvements. The Budget is for informational purposes only and is not binding on Landlord in any respect, and shall not create any limit on Aggregate Disbursements. Each disbursement of Construction Allowance funds by Landlord shall be deemed to be a "***Disbursement***" for purposes of this Lease. Other than the Disbursement being made to Tenant on the Effective Date, Tenant shall not be entitled to receive any other Disbursement from Landlord. Landlord shall make Disbursements directly to contractors in accordance with the terms of the Construction Agreements to which Landlord is a party.

6.2. Application of Construction Allowance. Landlord shall contribute the Construction Allowance funds toward the costs and expenses incurred in connection with the performance of the Building Improvements, in accordance with the Lease (including, but not limited to, reimbursement to Tenant for the costs and expenses set forth on Exhibit I attached hereto). Following the Punchlist Sign-off Date, Landlord shall have no commitment to disburse any additional Construction Allowance funds and Tenant shall have no right to receive any additional Construction Allowance funds for any purpose.

7. Assignment of Construction Agreements. Concurrently with the execution of the Lease, Tenant shall deliver to Landlord an assignment of Tenant's rights and obligations under that certain Architectural Services Agreement between Tenant and Architect, dated as of November , 2009 (the "***Architect's Agreement***"), executed by Tenant and acknowledged by Architect. Tenant shall also deliver to Landlord an estoppels certificate from the Architect certifying that there are no defaults, or events, that following notice and cure could become defaults, outstanding under the Architect's Agreement. Tenant shall use commercially reasonable efforts to assign to Landlord Tenant's rights and obligations under (a) all agreements with contractors, subcontractors,, material suppliers, architects, engineers or consultants (the "*Construction Agreements*") in existence as of the Effective Date that have been executed by Tenant, and (b) Tenant's interest in, to and under any Entitlements (to the extent that such assignment thereof would not cause a breach thereunder).

8. Completion of Building Improvements. The Building Improvements shall be deemed "***Complete***" at such time as (a) the Substantial Completion Date (as defined in the Lease) has occurred, (b) Landlord and Tenant shall have received evidence reasonably satisfactory to Landlord that (i) all Building

Improvements have been completed and paid for in full (which shall be evidenced by the Architect's certificate of completion), (ii) all certifications and approvals with respect to the Building Improvements that may be required from any Governmental Authority for the use and occupancy of the Premises have been obtained, (iii) a certificate from the Architect certifying that all work performed in, on or about the Premises is

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substantially in accordance with the Approved Plans, and (iv) the Punchlist Items have been completed and paid for in full, and (c) Landlord and Tenant shall have received complete drawing print sets and electronic CADD files on disc of all contract documents for work performed by their Architect and engineers in relation to the Building Improvements.

9. Miscellaneous.

9.1. Number; Headings. Where applicable in this Work Letter, the singular includes the plural and the masculine or neuter includes the masculine, feminine and neuter. The section headings of this Work Letter are not a part of this Work Letter and shall have no effect upon the construction or interpretation of any part hereof.

9.2. Attorneys' Fees. If either party commences an action against the other party arising out of or in connection with this Work Letter, then the prevailing party shall be entitled to have and recover from the other party reasonable attorneys' fees, charges and disbursements and costs of suit, in proportion [***] up to a maximum of 100%; *provided*, *however*, that in the case where the prevailing party is awarded any equitable relief, then the prevailing party may recover the full amount of such costs and attorney's fees. For example, if the prevailing party [***] and no equitable relief, but [***], and the prevailing party had two hundred thousand dollars ($200,000) in costs and attorneys' fees, then such prevailing party would be entitled to recover [***] of such costs and attorneys' fees. For purposes of clarity, prior to the Term Commencement Date, this provision is subject to the 89% Cap.

9.3. Time of Essence. Time is of the essence with respect to the performance of every provision of this Work Letter in which time of performance is a factor.

9.4. Covenant and Condition. Each provision of this Work Letter performable by Tenant shall be deemed both a covenant and a condition.

9.5. Withholding of Consent. Whenever consent or approval of either party is required, that party shall not unreasonably withhold, condition or delay such consent or approval, except as may be expressly set forth to the contrary.

9.6. Invalidity. Any provision of this Work Letter that shall prove to be invalid, void or illegal shall in no way affect, impair or invalidate any other provision hereof, and all other provisions of this Work Letter shall remain in full force and effect and shall be interpreted as if the invalid, void or illegal provision did not exist.

9.7. Interpretation. The language in all parts of this Work Letter shall be in all cases construed as a whole according to its fair meaning and not strictly for or against either Landlord or Tenant.

9.8. Successors. Each of the covenants, conditions and agreements herein contained shall inure to the benefit of and shall apply to and be binding upon the parties hereto and their respective heirs; legatees; devisees; executors; administrators; and permitted successors, assigns, sublessees. Nothing in this Section shall in any way alter the provisions of the Lease restricting assignment or subletting.

9.9. Governing Law. This Work Letter shall be governed by, construed and enforced in accordance with the laws of the State of California.

9.10. Power and Authority. Tenant guarantees, warrants and represents that the individual or individuals signing this Work Letter have the power, authority and legal capacity to sign this Work Letter on behalf of and to bind all entities, corporations, partnerships, limited liability companies, joint venturers or other organizations and entities on whose behalf said individual or individuals have signed.

9.11. Counterparts. This Work Letter may be executed in one or more counterparts, each of which, when taken together, shall constitute one and the same document.

9.12. Amendments; Waiver. No provision of this Work Letter may be modified, amended or supplemented except by an agreement in writing signed by Landlord and Tenant. The waiver by Landlord of any breach by Tenant of any term, covenant or condition herein contained shall not be deemed to be a waiver of any subsequent breach of the same or any other term, covenant or condition herein contained.

9.13. Waiver of Jury Trial. To the extent permitted by Applicable Laws, the parties waive trial by jury in any action, proceeding or counterclaim brought by the other party hereto related to matters arising out of or in any way connected with this Work Letter, the relationship between Landlord and Tenant, Tenant's use or occupancy of the Premises, or any claim of injury or damage related to this Work Letter or the Premises. This Section is not intended to and shall not be interpreted to act as a waiver to a trial by jury in any action by a party hereto against a third party.

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IN WITNESS WHEREOF, Landlord and Tenant have executed this Work Letter to be effective on the Effective Date.

LANDLORD:

BMR-GAZELLE COURT LLC
a Delaware limited liability company

By: _____
Name: John Bonanno
Title: Vice President, Development

TENANT:

ISIS PHARMACEUTICALS, INC.,
a Delaware corporation

By: _____
Name: B. Lynne Parshall
Title: Chief Operating Officer & Chief Financial Officer

SCHEDULE 1

SCHEDULE

[See Attached]

SCHEDULE 2

APPROVED DESIGN DEVELOPMENT PLANS

Isis Shell Design Development Set dated as of February 12, 2010

SCHEDULE 3

DRAFT DESIGN DEVELOPMENT TI PLANS

Isis Tenant Improvement Design Development Set dated as of March 23, 2010

SCHEDULE 4

BUDGET

[See Attached]

EXHIBIT C

TENANT'S PERSONAL PROPERTY

None as of the Effective Date.

EXHIBIT D

PURCHASE PRICE CALCULATION

The Purchase Option purchase price shall (i) equate to a [***] to Landlord as calculated over the period of time beginning when Landlord makes the initial Disbursement through the Purchase Option Closing Date and Tenant shall receive credit (as further described below) for all [***] and any [***] received under [***] received by Landlord pursuant to [***] of the Lease, [***] received by Landlord pursuant to Section [***] of the Lease, or [***] received by Landlord pursuant to Section [***] of the Lease, in each case paid through the Purchase Option Closing Date and (ii) include [***] Landlord [***] related to Landlord's sale of the Premises to Tenant pursuant to Tenant's exercise of the Purchase Option, subject to the attorney's fees cap set forth in Section 24.2.4 of the Lease.

The calculation will be made on a monthly basis using the [***] function, or an equivalent functionality, into which the PO Model shall be input, in which case the transcription of such PO Model shall be approved in writing by Landlord and Tenant, where all [***] paid by Tenant, and all [***] by Landlord during a given month, are treated to have occurred on the last calendar day of the month. Based on this monthly information, the model will calculate the terminal proceeds.

For the purposes of the Purchase Option purchase price calculation, the monthly cash flow calculations will include all [***] actually paid by Tenant through the Purchase Option Closing Date, including the portion of [***] pertaining to [***], and any [***] received under [***] proceeds received by Landlord pursuant to [***] of the Lease, [***] received by Landlord pursuant to [***] of the Lease, or [***] received by Landlord pursuant to Section [***] of the Lease, while the [***] made by Landlord will exclude the amounts related to [***].

Given that the transaction represents [***], any [***] related to the Premises are [***] and therefore are [***] for the calculation of the Purchase Option purchase price.

* * * * *

EXHIBIT E

OPERATING EXPENSE EXCLUSIONS

Notwithstanding anything contained in the Lease, the following are specifically excluded from property operating costs and Tenant shall have no obligation to pay directly or reimburse Landlord for all or any portion of the following except to the extent any of the following are caused by the actions or inactions of Tenant, or result from the failure of Tenant to comply with the terms of this Lease:

(i) costs incurred because Landlord actually violated the terms and conditions of this Lease or any other lease (to which Landlord is a party) for premises within the Premises, if any;

(ii) legal and auditing fees (other than (a) those fees expressly contemplated in the Lease to be paid as Additional Rent and (b) those fees reasonably incurred in connection with the maintenance and operation of all or any portion of the Premises), leasing commissions, advertising expenses, and other costs incurred in connection with the original leasing of the Premises (other than those fees expressly set forth in the Budget to be paid as part of the Construction Allowance) or future re-leasing of any portion of the Premises;

(iii) depreciation of the Premises or any other improvements situated within the project of which the Premises are a part;

(iv) any items for which Landlord is actually reimbursed by insurance or by direct reimbursement by Tenant or any other party;

(v) costs of repairs or other work necessitated by fire, windstorm or other casualty (excluding any deductibles) and/or costs of repair or other work necessitated by the exercise of the right of eminent domain, in each case to the extent insurance proceeds or a condemnation award, as applicable, is actually received by Landlord for such purposes;

(vi) other than any interest charges for capital improvements referred to in the Lease, any interest or payments on any financing obtained by Landlord with regard to the Premises, interest and penalties incurred as a result of Landlord's late payment of any property taxes or insurance procured by Landlord for the Premises unless such late payment is caused by a default by Tenant under the Lease or a failure to pay Additional Rent as required pursuant to the Lease;

(vii) overhead and profit increment paid to Landlord or to subsidiaries or affiliates of Landlord for goods and/or services in the Premises to the extent the same exceeds the costs of such by unaffiliated third parties on a competitive basis; or any costs included in property operating expenses representing an amount paid to a person, firm, corporation or other entity related to Landlord which is in excess of the amount which would have been paid in the absence of such relationship.

EXHIBIT F

MEMORANDUM OF LEASE

Recording Requested By:

When Recorded Return To:

LATHAM & WATKINS LLP
Attn: Robert Frances, Esq.
600 West Broadway, 18th Floor
San Diego, California 92101-3375

THE AREA ABOVE IS RESERVED FOR RECORDER'S USE

MEMORANDUM OF LEASE

This Memorandum of Lease ("Memorandum") is made and entered into as of March , 2010, by and between BMR-GAZELLE COURT LLC, a Delaware limited liability company ("Landlord"), and ISIS PHARMACEUTICALS, INC., a Delaware corporation ("Tenant"), in connection with that certain

real property located in Carlsbad, California, and more particularly described on **Exhibit "A"** attached hereto and incorporated herein by reference (together with any improvements now or hereafter constructed thereon, the "Premises").

1. Lease. Pursuant to the terms and provisions of that certain unrecorded Lease by and between Landlord and Tenant, dated March 30, 2010 (the "Lease"), Tenant leased the Premises from Landlord. Capitalized terms used herein but not otherwise defined shall have the meanings ascribed thereto in the Lease.

2. Lease Term. The Lease shall take effect on March 30, 2010. The term of the Lease shall be for two hundred forty (240) months commencing on the Substantial Completion Date (as defined in the Lease) (the "Term Commencement Date") and ending on the date that is two hundred forty (240) months after the Term Commencement Date (the "Lease Term"), subject to earlier termination of the Lease as provided therein; provided, however, that the Lease provides Tenant with four (4) options to extend the Lease Term, as further described in the Article 36 of the Lease.

3. Purchase Option. The Lease grants Tenant the option to purchase the Premises from Landlord at the end of the following respective Lease Years: the fifth (5th), sixth (6th), seventh (7th), eighth (8th), ninth (9th), fifteenth (15th) and twentieth (20th) Lease Year, subject to and in accordance with Section 24.2 of the Lease.

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4. Right of First Negotiation. The Lease grants Tenant the right of first negotiation with respect to any sale of the Premises by Landlord to a third party, subject to and in accordance with Section 24.3 of the Lease.

5. No Effect on Lease. The parties have prepared, signed, and acknowledged this Memorandum solely for recording purposes. This Memorandum does not modify, increase, decrease, or in any other way affect any party's rights, duties, or obligations under the Lease. Landlord and Tenant each has rights, duties, and obligations (and conditions to its rights) under the Lease but not stated in this Memorandum. If the provisions of the Lease and the provisions of this Memorandum conflict, then the provisions of the Lease shall govern. Nothing in this Memorandum constitutes any representation or warranty by either party. To the extent, if any, that the Lease limits the liability of either Landlord or Tenant, such limitation also applies to any such liability under this Memorandum.

6. Successors and Assigns. The Lease and this Memorandum shall bind and benefit the parties hereto and their successors and assigns.

7. Termination. This Memorandum shall automatically terminate and be of no force or effect upon any termination of the Lease. Within fifteen (15) days following such termination, Tenant will provide to Landlord an executed and acknowledged Quitclaim Deed, releasing and quitclaiming all right, title and interest in and to the Property, specifically including any interest pursuant to the Lease.

8. Counterparts. This Memorandum may be executed in any number of counterparts, each of which shall be deemed to be an original, and all of such counterparts shall constitute one agreement. To facilitate the execution of this Memorandum, the parties may execute and exchange by telephone facsimile or by other electronic methods (including email) counterparts of this Memorandum or the signature pages hereto. Signatures to this Memorandum transmitted electronically or by telecopy shall be valid and effective to bind the party so signing. Each party hereto agrees to promptly deliver to the other party an executed original to this Memorandum with its actual signature, but a failure to do so shall not affect the enforceability of this Memorandum, it being expressly agreed that each party to this Memorandum shall be bound by its own telecopied or electronically delivered signature and shall accept the telecopied or electronically delivered signature of the other parties to this Memorandum.

[Remainder of Page Left Intentionally Blank]

IN WITNESS WHEREOF, Landlord and Tenant have executed this Memorandum of Ground Lease as of the date first above written.

LANDLORD:

BMR-GAZELLE COURT LLC

By: _____
Name: John Bonanno
Title: Vice President, Development

TENANT:

ISIS PHARMACEUTICALS, INC.

By: _____
Name: B. Lynne Parshall
Title: Chief Operating Officer & Chief Financial Officer

[MEMORANDUM OF LEASE SIGNATURE PAGE]

STATE OF CALIFORNIA }
COUNTY OF } *S.S.*

On , before me, , a Notary Public in and for said County and State, personally appeared,

, who proved to me on the basis of satisfactory evidence to be the person(s) whose name(s) is/are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity(ies), and that by his/her/their signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

I certify under PENALTY OF PERJURY under the laws of the State of California that the foregoing paragraph is true and correct.

WITNESS my hand and official seal.

Signature: _____

(Notary Seal)

[MEMORANDUM OF LEASE ACKNOWLEDGMENT PAGE]

STATE OF CALIFORNIA }
COUNTY OF } *S.S.*

On , before me, , a Notary Public in and for said County and State, personally appeared,

, who proved to me on the basis of satisfactory evidence to be the person(s) whose name(s) is/are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity(ies), and that by his/her/their signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

I certify under PENALTY OF PERJURY under the laws of the State of California that the foregoing paragraph is true and correct.

WITNESS my hand and official seal.

Signature: _____

(Notary Seal)

EXHIBIT "A"

Description of the Property

PARCEL 1:
PARCEL "A" OF CERTIFICATE OF COMPLIANCE NO. ADJ 09-05 RECORDED JANUARY 19, 2010 AS INSTRUMENT NO. 2010-0024854 OF OFFICIAL RECORDS, DESCRIBED AS FOLLOWS:
LOT 14 OF CARLSBAD TRACT NO. 97-13-02, ACCORDING TO MAP THEREOF NO. 15505, IN THE CITY OF CARLSBAD, COUNTY OF SAN DIEGO, STATE OF CALIFORNIA, RECORDED IN THE OFFICE OF THE COUNTY RECORDER OF SAN DIEGO COUNTY ON JANUARY 23, 2007 AS FILE NO. 2007-0047588, TOGETHER WITH A PORTION OF LOT 'B' OF RANCHO AGUA HEDIONDA, IN THE CITY OF CARLSBAD, COUNTY OF SAN DIEGO, STATE OF CALIFORNIA, ACCORDING TO MAP THEREOF NO. 823, FILED IN THE OFFICE OF THE COUNTY RECORDER OF SAN DIEGO COUNTY, NOVEMBER 16, 1896, BEING MORE PARTICULARLY DESCRIBED AS FOLLOWS:

BEGINNING AT THE NORTHWEST CORNER OF SAID LOT 14; THENCE, ALONG THE NORTH LINE OF SAID LOT 14, NORTH 89°09'41" EAST 629.31 FEET; THENCE SOUTH 00°31'59" WEST 8.11 FEET; THENCE NORTH 89°53'58" EAST 392.46 FEET; THENCE NORTH 53°13'30" EAST 15.15 FEET; THENCE SOUTH 56°49'30" EAST 85.95 FEET TO THE NORTHEAST CORNER OF SAID LOT 14, SAID CORNER BEING ON A NON-TANGENT 264.00 FOOT RADIUS CURVE CONCAVE NORTHWESTERLY, THE RADIAL LINE TO SAID POINT BEARS SOUTH 56°49'30" EAST; THENCE, ALONG THE EAST LINE OF SAID LOT 14, SOUTHWESTERLY ALONG SAID CURVE THROUGH A CENTRAL ANGLE OF 5°50'08" AN ARC DISTANCE OF DISTANCE OF 26.89; THENCE, TANGENT TO SAID CURVE, SOUTH 39°00'38" WEST 329.54 FEET TO THE BEGINNING OF A TANGENT 736.00 FOOT RADIUS CURVE CONCAVE SOUTHEASTERLY; THENCE SOUTHWESTERLY ALONG SAID CURVE THROUGH A CENTRAL ANGLE OF 25°07'33" A DISTANCE OF 322.76 TO THE SOUTHEAST CORNER OF SAID LOT 14, SAID CORNER ALSO BEING A POINT ON THE SUBDIVISION BOUNDARY OF MAP NO. 14926; THENCE, ALONG THE SOUTH LINE OF SAID LOT 14 AND THE BOUNDARY OF SAID MAP NO. 14926, NON-TANGENT TO SAID CURVE NORTH 52°33'23" WEST 148.70 FEET; THENCE SOUTH 48°06'30" WEST, 21.89 FEET TO THE BEGINNING OF A 100.00 FOOT RADIUS CURVE CONCAVE NORTHWESTERLY; THENCE SOUTHWESTERLY ALONG SAID CURVE THROUGH A CENTRAL ANGLE OF 34°22'48" AN ARC DISTANCE OF 60.00 FEET; THENCE 82°29'18" WEST 147.20 FEET; THENCE NORTH 89°14'55" WEST 410.06 FEET TO THE SOUTHWEST CORNER OF SAID LOT 14; THENCE, LEAVING SAID LOT 14 AND CONTINUING ALONG THE BOUNDARY OF SAID MAP NO. 14926, SOUTH 29°36'38" WEST 51.14 FEET; THENCE NORTH 77°38'20" WEST 216.59 FEET; THENCE, LEAVING THE BOUNDARY OF SAID MAP NO. 14926, NORTH 43°05'58" EAST 78.45 FEET; THENCE NORTH 01°47'45" EAST 442.55 FEET TO A POINT ON THE SOUTHERLY BOUNDARY OF THAT PUBLIC STREET AND UTILITY EASEMENT RECORDED JANUARY 23, 2007 AS FILE NO. 2007-0047586, SAID POINT BEING ON A NON-TANGENT 836.00 FOOT RADIUS CURVE CONCAVE NORTHERLY, A RADIAL LINE TO SAID POINT BEARS SOUTH 23°00'29" WEST; THENCE, EASTERLY ALONG SAID EASEMENT AND SAID CURVE, THROUGH A CENTRAL ANGLE OF 10°54'11" AN ARC DISTANCE OF 159.09 TO THE BEGINNING OF A COMPOUND 56.00 FOOT RADIUS CURVE CONCAVE WESTERLY; THENCE NORTHERLY ALONG SAID CURVE THROUGH A CENTRAL ANGLE OF 181°26'49" AN ARC DISTANCE OF 177.34 TO THE POINT OF BEGINNING.

PARCEL 2:
AN EASEMENT FOR A PRIVATE DRAINAGE OVER AND ACROSS LOT 4 OF CARLSBAD TRACT NO. 97-13-01, CARLSBAD OAKS NORTH PHASE 1, IN THE CITY OF CARLSBAD, COUNTY OF SAN DIEGO, STATE OF CALIFORNIA, ACCORDING TO MAP THEREOF NO. 14926, RECORDED IN THE OFFICE OF THE COUNTY RECORDER OF SAN DIEGO COUNTY ON DECEMBER 15, 2004, AS CREATED BY EASEMENT AGREEMENT EXECUTED BY KILROY REALTY FINANCE PARTNERSHIP, L.P., A DELAWARE LIMITED PARTNERSHIP, TECHBILT CONSTRUCTION CORP., A CALIFORNIA CORPORATION AND CARLSBAD OAKS NORTH PARTNERS, L.P., A CALIFORNIA LIMITED PARTNERSHIP, DATED JANUARY 20, 2010 AND RECORDED JANUARY 29, 2010 AS INSTRUMENT NO. 2010-0047608 OF OFFICIAL RECORDS.

APN: 209-120-11 and a portion of 209-120-17

[MEMORANDUM OF LEASE ACKNOWLEDGMENT PAGE]

EXHIBIT G

FORM PURCHASE AND SALE AGREEMENT

[See Attached]

AGREEMENT OF SALE]

THIS AGREEMENT OF SALE (this "***Agreement***") is made the day of , 20 (the "***Effective Date***"), by and between **BMR-GAZELLE COURT LLC,** a Delaware limited liability company ("***Seller***"), and **ISIS PHARMACEUTICALS, INC.,** a Delaware corporation ("***Buyer***"). Seller and Buyer are sometimes hereinafter referred to collectively as the "***parties***".

W I T N E S S E T H

1. **Sale of Premises.**

A. Purchase and Sale. Subject to all of the terms and conditions of this Agreement, Seller agrees to sell and convey to Buyer, and Buyer agrees to purchase from Seller, any and all of Seller's right, title and interest in and to the following:

(i) the land located at Gazelle Court, Carlsbad, California, as more fully described in Exhibit "A" attached hereto and made a part hereof, together with all strips and gores and any land lying in the bed of any street, road or alley, open or proposed, adjoining such real property (collectively, the "***Land***");

(ii) all and singular the rights, benefits, privileges, easements, tenements, hereditaments, and appurtenances thereon or in anyway appertaining to the Land (collectively, the "***Appurtenant Rights***");

(iii) buildings, structures, fixtures, systems, improvements, topsoil, trees, shrubbery and landscaping situated on, in or under or used in connection with the land (collectively, the "***Improvements***");

(iv) all right, title and interest of Seller, if any, in and to all tangible personal property now or hereafter located on, or used exclusively in connection with, the operation, ownership, maintenance, occupancy or improvement of the Land (collectively, the ***"Tangible Personal Property"***; and

(v) all right, title and interest of Seller, if any, in and to all intangible personal property now or hereafter used exclusively in connection with the operation, ownership, maintenance, management, or occupancy of the Land or Improvements (to the extent assignable); the plans and specifications for the Improvements (to the extent assignable); warranties, indemnities, guaranties (express or implied), applications, permits, authorizations, approvals and licenses (to the extent applicable in any way to the above referenced Land, Improvements or the Tangible Personal Property and assignable); insurance proceeds received by (or owed to) Seller which relate to damage to the Land or Improvements caused by a casualty that has occurred prior to the Closing Date and for which restoration has not previously occurred, but only to the extent that such proceeds have not been applied by Seller prior to the Closing Date towards the cost of (a) pursuit or settlement of the applicable insurance claim, (b) the clearing of debris or other expenses associated with securing the Land or Improvements, or (c) restoration of the Land or Improvements; and condemnation awards or claims thereto (collectively, the "***Intangible Property***").

B. Premises Defined. The Land, the Appurtenant Rights, the Improvements, the Tangible Personal Property and the Intangible Property are hereinafter referred to as the "***Premises***".

2. **Purchase Price.** The purchase price for the Premises (the "***Purchase Price***") shall be Dollars ($), payable as follows:

A. Deposit. Concurrently with the execution and delivery of this Agreement, (i) the parties shall establish an escrow (the "***Escrow***") with [Chicago Title Insurance Company, 2365 Northside Drive, 6th Floor, San Diego, CA 92108, Attn: Renee Marshall] (the "***Title Company***"), (ii) the parties shall deposit with the Title Company a fully executed original of this Agreement, and (iii) Buyer shall deposit with the Title Company a sum equal to

[Dollars ($)] **[INSERT AMOUNT THAT IS [***] OF THE PURCHASE PRICE]** in good funds either by certified bank or cashier's check or by federal wire transfer (such funds, together with all interest accrued thereon while held in Escrow, the "***Deposit***"). The Deposit shall be held in escrow by the Title Company in a federally insured, interest bearing account in accordance with the laws of the State of California and the provisions of this Agreement. If this Agreement is terminated pursuant to Section 7 hereof, the Deposit shall be paid to either Buyer or Seller in accordance with the provisions of Section 7. If the sale of the Premises is consummated, the Deposit shall be released to Seller and shall be credited against the Purchase Price.

B. Payment of Purchase Price. At Closing, the Deposit shall be released to Seller, and Buyer shall pay to Seller through Escrow in the manner described herein the balance of the Purchase Price, as adjusted for prorations and other adjustments provided herein.

3. **Condition of Title.**

A. Title Review. Buyer acknowledges that it has been provided with the right and opportunity to review and investigate any and all conditions and aspect of title to the Premises deemed necessary or desirable by Buyer for purposes of evaluating the transactions contemplated hereby.

B. Title Examination. Buyer hereby acknowledges that it approves all the encumbrances and exceptions to title embodied in the Permitted Exceptions (as defined below), and Buyer shall take title to the Premises subject to all such Permitted Exceptions (as defined below); provided, however, that Seller shall cause any liens granted by Seller and encumbering the Premises to secure the repayment of borrowed money to be removed from title or otherwise insured over by the Title Company. Without limiting the effect of the foregoing, the parties acknowledge and agree that the term "***Permitted Exceptions***" shall include the following:

(i) the title encumbrances described on Exhibit F attached hereto;

(ii) all covenants, conditions, restrictions, reservations, rights, rights of way, dedications, offers of dedication, encumbrances, liens and easements, in each case whether filed in the applicable public records or as would be apparent from an inspection or accurate survey of the Premises, except in each case to the extent that the same are granted or caused by Seller in a manner that would constitute a breach under the Lease;

(iii) the rights of tenants or other occupants under any leases, licenses, and occupancy agreements granted by any person or entity other than Seller, including all amendments or modifications thereto or supplements thereof, covering all or any portion of the Premises;

(iv) the lien of all ad valorem real estate taxes and assessments;

(v) all liens and encumbrances with respect to the Premises which were granted by, or which arise in connection with the acts or omissions of, Buyer or any of Buyer's agents, contractors, affiliates, invitees, or any other party that Buyer has permitted to use or occupy the Land or Improvements from and after the Effective Date of the Lease (as such term is defined in the Lease);

(vi) local, state and federal laws, ordinances or governmental regulations, including but not limited to building and zoning laws, ordinances and regulations, now or hereafter in effect relating to the Premises; and

(vii) those matters which would be disclosed by an accurate survey or inspection of the Premises.

C. Conveyance of Title. At Closing, Seller shall convey and transfer, or cause to be conveyed or transferred, to Buyer all of Seller's right, title and interest in and to the Premises, subject to the Permitted Exceptions.

D. Covenants of Seller. Seller, as Landlord, and Buyer, as tenant, are parties to that certain Lease Agreement, dated March 30, 2010 (the "***Lease***") pursuant to which Buyer leases the Premises and is responsible for, among other things, its repair, upkeep and maintenance. Accordingly, Seller has not undertaken to either manage or operate the Premises in any particular way prior to Closing, or deliver the Premises at Closing in any particular condition. During the period from and after the Effective Date until the date that Closing occurs, Seller (i) shall fully and timely perform its obligations under the Lease, and (ii) shall not, without Buyer's consent (which will not be unreasonably withheld, conditioned or delayed), grant any new liens or encumbrances against the Premises or take any action which would have a material adverse effect on (a) the use of the Premises in the manner in which it is being used as of the Effective Date, or (b) the value of the Premises.

4. **Closing.** The consummation of the purchase and sale of the Premises contemplated by this Agreement (the "***Closing***") shall take place on [, 20] (the "***Closing Date***") at [1:00 PM local time] through the Escrow administered by the Title Company, or such other time and place as Seller and Buyer agree to in writing. **[NOTE: TO BE**

DETERMINED IN ACCORDANCE WITH SECTIONS 19.1.4 OR 24.2 OF THE LEASE, AS APPLICABLE].

A. Conditions to Seller's Obligation to Close. The obligation of Seller to consummate the transactions contemplated hereunder shall be contingent upon the following:

(i) Representations. Buyer's representations and warranties contained herein shall be materially true and correct as of the date of this Agreement;

(ii) Performance. All deliveries to be made by Buyer at Closing have been tendered, and Buyer shall have performed all of the other obligations to be performed by Buyer under this Agreement; and

(iii) Moratorium. No moratorium, statute or regulation of any governmental agency or order or ruling of any court has been enacted, adopted, or issued which would adversely affect Buyer's ability to purchase the Property from Seller.

B. Conditions to Buyer's Obligation to Close. The obligation of Buyer to consummate the transactions contemplated hereunder shall be contingent upon the following:

(i) Representations. Seller's representations and warranties contained herein shall be materially true and correct as of the date of this Agreement;

(ii) Performance. All deliveries to be made by Seller at Closing have been tendered, and Seller shall have performed all of the other obligations to be performed by Seller under this Agreement;

(iii) Title. Upon the sole condition of payment of the premium, at Closing, the Title Company shall have irrevocably and unconditionally committed to issue to Buyer an ALTA Owner's Policy of title insurance, with extended coverage (i.e., with ALTA General Exceptions deleted), dated as of the date and time of the recording of the Deed (as defined below), in the amount of the Purchase Price, insuring Buyer as owner of good, marketable and indefeasible fee simple title to the Property, subject only to the Permitted Exceptions; provided, however, that notwithstanding the foregoing or any other provision of this Agreement to the contrary, the parties agree that Seller shall not be required to provide any indemnities, representations, warranties or affidavits to the Title Company; and

(iv) Moratorium. No moratorium, statute or regulation of any governmental agency or order or ruling of any court has been enacted, adopted, or issued which would adversely affect Seller's ability to sell the Property to Buyer.

C. Failure of Condition Precedent. If any condition to such party's obligation to proceed with the Closing hereunder has not been satisfied as of the Closoing Date; each non-defaulting party may, in its sole discretion, either (i) terminate this Agreement by delivering written notice to the other party, or (ii) elect to close, notwithstanding the non-satisfaction of such condition, in which event such party shall be deemed to have waived any such condition.

5. **Provisions With Respect to Closing.**

A. Deliveries by Seller. At least one (1) business day prior to the Closing Date, Seller shall deliver, or cause to be delivered, to the Title Company, to be held in Escrow pending Closing, each of the following:

(i) Deed. One (1) original Grant Deed, duly executed and acknowledged by Seller, substantially in the form of Exhibit "B" attached hereto (the "***Deed***");

(ii) Bill of Sale and Assignment of Warranties. Two (2) original counterparts of a Bill of Sale and Assignment and Assumption of Warranties, duly executed by Seller, substantially in the form of Exhibit "C" attached hereto ("***Bill of Sale and Assignment of Warranties***");

(iii) Termination of Lease. Two (2) original counterparts of a Termination of Lease Agreement, duly executed by Seller substantially in the form of Exhibit "D" attached hereto ("***Lease Termination***");

(iv) FIRPTA Affidavit. One (1) original Certificate Regarding Foreign Investment in Real Property Tax Act, duly executed and acknowledged by Seller, substantially in the form of Exhibit "E" attached hereto.; and

(v) Closing Statement. An executed closing statement consistent with this Agreement and in a form requested by the Title Company.

B. Deliveries by Buyer. At least one (1) business day prior to the Closing Date, Buyer shall deliver, or cause to be delivered, to the Title Company, to be held in Escrow pending Closing, each of the following:

(i) Funds. The balance of the Purchase Price, as adjusted for prorations and other adjustments provided herein;

(ii) Bill of Sale and Assignment of Warranties. Two (2) original counterparts of the Bill of Sale and Assignment of Warranties, duly executed by Buyer;

(iii) Termination of Lease. Two (2) original counterparts of the Lease Termination, duly executed by Buyer;

(iv) Release. A release of claims, duly executed and acknowledged by Buyer that contains the same disclaimers and release as set forth in Section 11, except such release will be dated as of the Closing Date (the "***Release***"); and

(v) Closing Statement. An executed closing statement consistent with this Agreement and in a form requested by the Title Company.

6. **Closing Costs; Taxes; Apportionments.**

A. Buyer shall pay: (i) the fees of any counsel representing Buyer in connection with the transaction contemplated by this Agreement (the "***Transaction***"); (ii) the fees of any counsel representing Seller in connection with the Transaction (provided, however, that Buyer shall not be required to pay such fees in excess of $25,000 (as such amount shall be adjusted by multiplying $25,000 by the CPI Adjustment Factor described below)); (iii) the escrow fee, if any, which may be charged by the Title Company; (iv) the costs of any title reports, commitments or policies that Buyer may elect to obtain; (v) the cost of any survey that Buyer may elect to obtain; (v) all of the recording fees in connection with the sale transaction, and (vi) any transfer and sales

taxes (but excluding Seller's federal or state income, franchise, inheritance or estate taxes) that may arise in connection with the Transaction. As used herein, the "***CPI Adjustment Factor***" means, as of Closing Date, the greater of (a) the CPI for such date divided by the CPI for the Effective Date of the Lease; and (b) 1.00. As used herein, "***CPI***" means the United States Department of Labor, Bureau of Labor Statistics "Consumer Price Index" for All Urban Consumers (CPI-U) published for the Los Angeles-Riverside-Orange County, CA, Metropolitan Statistical Area, with a base of 1982-1984 = 100. If the CPI ceases to be published, with no successor index, then the parties shall reasonably agree upon a reasonable substitute index. The CPI for any date means the CPI last published before the calendar month that includes such date.

B. Seller shall pay the fees of any counsel representing Seller to the extent that such fees exceed the amount of Seller's legal fees for which Buyer is responsible pursuant to Section 6(A)(ii) above.

C. Prorations. If the Purchase Price is received by Seller's depository bank in time to credit to Seller's account on the Closing Date, the day of Closing shall belong to Buyer and all prorations hereinafter provided to be made as of the Closing shall each be made as of the end of the day before the Closing Date. If the cash portion of the Purchase Price is not so received by Seller's depository bank on the Closing Date, then the day of Closing shall belong to Seller and such proration shall be made as of the end of the day that is the Closing Date. In each such proration set forth below, the portion thereof applicable to periods beginning as of Closing shall be credited to Buyer or charged to Buyer as applicable and the portion thereof applicable to periods ending as of Closing shall be credited to Seller or charged to Seller as applicable. The parties acknowledge and agree that the Lease is a fully triple net lease such that Buyer, as tenant, is responsible to pay directly, or reimburse Seller for, any and all expenses incident to the ownership, operation and maintenance of the Premises, in each case as required under the Lease. As a result, the parties shall not engage in normal and customary prorations. However, at Closing, Buyer shall pay or credit to Seller any and all of the following: (i) all Rent (as defined in the Lease) owing from Buyer, as tenant, to Seller (such amounts, "***Rental Amounts***") under the Lease for the portion of the month in which closing occurs occurring prior to Closing and any period prior to Closing to the extent not previously paid by Buyer to Seller, including, but not limited to, any rental delinquencies; and (ii) all sums advanced or paid by Seller for real estate taxes, operating expenses, general assessments or special assessments related to the Premises for any period prior to or subsequent to the Closing to the extent not previously paid or reimbursed by Buyer, including, but not limited to, real estate taxes paid by Seller with respect to any period

prior to or subsequent to the Closing and not yet reimbursed. At Closing, Seller shall credit to Buyer any Rental Amounts paid by Buyer that are allocable to the period from and after Closing; provided, however, that Seller shall retain all amounts of additional rent previously paid by Buyer to Seller on account of common area maintenance expenses, real estate taxes, insurance expenses or other expenses to the extent incurred by Seller on account of expenses allocable to the Premises prior to or after Closing and previously paid by Seller.

D. Final Adjustment After Closing. In the event that final bills are not available or cannot be issued prior to Closing for any item being prorated under this Article 6, then Buyer and Seller agree to allocate such items on a fair and equitable basis as estimated based on the previous year's amounts, with a true-up and final adjustment to be made as soon as reasonably possible after the Closing but no later than [six (6)] months after Closing. Payments in connection with the final adjustment shall be due within thirty (30) days after receipt of written notice. Each party shall have reasonable access to, and the right to inspect and audit, the other party's books to confirm the final prorations.

7. **Failure to Close; Defaults.**

A. Buyer's Default. Provided that Seller has materially complied with its obligations hereunder and the conditions set forth in Section 4B have been satisfied, if Buyer fails to complete the Closing in accordance with the terms of this Agreement, then in addition to (i) any rights or remedies that Seller may have in connection therewith under the Lease, and (ii) any loss of rights that Buyer may incur in connection therewith and under the Lease (collectively, the "***Lease Implications***"), the Deposit shall be retained by Seller as liquidated and agreed damages for such breach, which shall be Seller's sole and exclusive right and remedy under this Agreement for such breach, whereupon this Agreement shall become null and void and neither party hereto shall have any further rights, liabilities or obligations hereunder except those obligations which expressly survive termination

THE PARTIES ACKNOWLEDGE THAT SELLER'S ACTUAL DAMAGES IN THE EVENT THE SALE IS NOT CONSUMMATED ARE EXTREMELY DIFFICULT OR IMPRACTICABLE TO DETERMINE AT THE EFFECTIVE DATE. THEREFORE, BY SEPARATELY EXECUTING THIS SECTION 7(A) BELOW, THE PARTIES ACKNOWLEDGE THAT THE AMOUNT OF THE DEPOSIT HAS BEEN AGREED UPON, AFTER NEGOTIATION, AS THE PARTIES' REASONABLE ESTIMATE OF SELLER'S DAMAGES AND NOT A PENALTY, AND SHALL (ASIDE FROM THE LEASE IMPLICATIONS, WHICH SHALL NOT BE LIMITED IN ANY WAY BY THIS SECTION BE SELLER'S SOLE AND EXCLUSIVE REMEDY AGAINST BUYER ARISING FROM A FAILURE OF THE SALE TO CLOSE. IN ADDITION, BUYER SHALL PAY ALL COSTS AND EXPENSES ALLOCABLE TO BUYER PURSUANT TO SECTION 6(A), AS WELL AS ALL TITLE AND ESCROW CANCELLATION CHARGES. NOTWITHSTANDING THE FOREGOING, IN NO EVENT SHALL THIS SECTION 7(A) LIMIT THE DAMAGES RECOVERABLE BY EITHER PARTY AGAINST THE OTHER PARTY DUE TO THE OTHER PARTY'S OBLIGATION TO INDEMNIFY SUCH PARTY IN ACCORDANCE WITH SECTION 14 OF THIS AGREEMENT. BY SEPARATELY EXECUTING THIS SECTION 7(A). BELOW, BUYER AND SELLER ACKNOWLEDGE THAT THEY HAVE

READ AND UNDERSTOOD THE ABOVE PROVISION COVERING LIQUIDATED DAMAGES, AND THAT EACH PARTY WAS REPRESENTED BY COUNSEL WHO EXPLAINED THE CONSEQUENCES OF THIS LIQUIDATED DAMAGES PROVISION AT THE TIME THIS AGREEMENT WAS EXECUTED.

BMR-GAZELLE COURT LLC

By: _____

Name: _____

ISIS PHARMACEUTICALS, INC.

By: _____

Name: _____

Title: _____ Title: _____

B. Seller's Default. In the event that Seller shall fail to perform the acts required by this Agreement to be performed by it prior to or as of the Closing for any reason, or the conditions set forth in Section 4B were not satisfied for any reason, Buyer shall be entitled, as its sole and exclusive remedy, to (i) receive the return of the Deposit, which return shall operate to terminate this Agreement and release Seller from any and all liability hereunder, or (ii) to enforce specific performance of Seller's obligation to convey the Premises to Buyer as contemplated by this Agreement, it being understood that the remedy of specific performance shall not be available to enforce any other obligation of Seller hereunder. Buyer shall be deemed to have elected to terminate this Agreement and receive the return of the Deposit as its sole and exclusive remedy if Buyer fails to file suit for specific performance against Seller in a court having jurisdiction in the county and state in which the Premises is located within sixty (60) days following the scheduled Closing Date.

8. **Seller's Representations, Warranties and Covenants.** Seller hereby represents, warrants and covenants to Buyer, as of the Effective Date, as follows:

A. Seller has full capacity, power and authority to execute and deliver this Agreement and to perform its obligations hereunder.

B. This Agreement, and all other instruments and documents to be executed and delivered by Seller to Buyer hereunder or pursuant hereto, have been or will be duly executed and delivered by Seller and constitute (or will constitute, as to those instruments and documents to be executed and delivered) the legal, valid and binding obligations of Seller enforceable against Seller in accordance with their respective terms, subject to applicable bankruptcy, insolvency, fraudulent conveyance, reorganization, moratorium and similar laws affecting creditors' rights and remedies generally and general principals of equity.

C. There is no suit, action or proceeding pending or to the knowledge of Seller threatened against Seller before or by any court, administrative agency or other governmental or quasi-governmental authority, (i) affecting the Premises or (ii) which brings into question the validity of this Agreement or the Transaction.

9. **Buyer's Representations, Warranties and Covenants.** Buyer hereby represents, warrants and covenants to Seller, as of the Effective Date, as follows:

A. Buyer has full capacity, power and authority to execute and deliver this Agreement and to perform all of its obligations hereunder.

B. This Agreement and all other instruments and documents to be executed and delivered by Buyer to Seller hereunder or pursuant hereto have been or will be duly executed and delivered by Buyer and constitute (or will constitute, as to those instruments and documents to be executed and delivered) the legal, valid and binding obligations of Buyer enforceable against Buyer in accordance with their respective terms.

C. There is no suit, action or proceeding pending or to the knowledge of Buyer threatened against Buyer or affecting the Premises before or by any court, administrative agency or other governmental or quasi-governmental authority, or which brings into question the validity of this Agreement or the Transaction.

10. **Investigations.**

A. Buyer acknowledges that it (i) is familiar with the Premises, (ii) has been given an opportunity to inspect the Premises and (iii) has completed all of its inspections with respect to the condition of the Premises as of the Effective Date.

11. **Disclaimers and Warranties.**

A. AS IS SALE; DISCLAIMERS. WITH RESPECT TO CLAUSES (i) THROUGH (iv) BELOW, EXCEPT IN THE CASE OF A BREACH BY SELLER OF THE REPRESENTATIONS AND WARRANTIES CONTAINED IN SECTION 8, AND EXCEPT FOR SELLER'S BREACH OF ITS COVENANT SET FORTH IN SECTION 3D:

i. SELLER IS NOT MAKING, AND HAS NOT AT ANY TIME MADE, ANY WARRANTIES OR REPRESENTATIONS OF ANY KIND OR CHARACTER, EXPRESS OR IMPLIED, WITH RESPECT TO THE PREMISES, INCLUDING, BUT NOT LIMITED TO, ANY WARRANTIES OR REPRESENTATIONS AS TO HABITABILITY, MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE.

ii. UPON CLOSING SELLER SHALL SELL AND CONVEY TO BUYER, AND BUYER SHALL ACCEPT, THE PREMISES "AS IS, WHERE IS, WITH ALL FAULTS". BUYER HAS NOT RELIED AND WILL NOT RELY ON, AND SELLER IS NOT LIABLE FOR OR BOUND BY, ANY EXPRESS OR IMPLIED WARRANTIES, GUARANTIES, STATEMENTS, REPRESENTATIONS OR INFORMATION PERTAINING

TO THE PREMISES OR RELATING THERETO MADE OR FURNISHED BY SELLER OR ANY REAL ESTATE BROKER OR AGENT REPRESENTING OR PURPORTING TO REPRESENT SELLER, TO WHOMEVER MADE OR GIVEN, DIRECTLY OR INDIRECTLY, ORALLY OR IN WRITING. ALL MATERIALS, DATA AND INFORMATION DELIVERED BY SELLER TO BUYER, OR OTHERWISE MADE AVAILABLE TO BUYER, IN CONNECTION WITH THE TRANSACTION CONTEMPLATED HEREBY ARE PROVIDED TO BUYER AS A CONVENIENCE ONLY AND ANY RELIANCE ON OR USE OF SUCH MATERIALS, DATA OR INFORMATION BY BUYER SHALL BE AT THE SOLE RISK OF BUYER. NEITHER SELLER, NOR ANY AFFILIATE OF SELLER, NOR THE PERSON OR ENTITY WHICH PREPARED ANY REPORT OR REPORTS MADE AVAILABLE BY SELLER TO BUYER SHALL HAVE ANY LIABILITY TO BUYER FOR ANY INACCURACY IN OR OMISSION FROM ANY SUCH

REPORTS. BUYER ACKNOWLEDGES THAT THE PURCHASE PRICE REFLECTS AND TAKES INTO ACCOUNT THAT THE PREMISES IS BEING SOLD "AS IS."

iii. BUYER REPRESENTS AND COVENANTS TO SELLER THAT BUYER HAS CONDUCTED SUCH INVESTIGATIONS OF THE PREMISES, INCLUDING BUT NOT LIMITED TO, THE PHYSICAL AND ENVIRONMENTAL CONDITIONS THEREOF, AS BUYER DEEMS NECESSARY OR DESIRABLE TO SATISFY ITSELF AS TO THE CONDITION OF THE PREMISES AND THE EXISTENCE OR NONEXISTENCE OF, OR CURATIVE ACTION TO BE TAKEN WITH RESPECT TO, ANY HAZARDOUS OR TOXIC SUBSTANCES ON OR DISCHARGED FROM THE PREMISES, AND WILL RELY SOLELY UPON SAME AND NOT UPON ANY INFORMATION PROVIDED BY OR ON BEHALF OF SELLER OR ITS AGENTS OR EMPLOYEES WITH RESPECT THERETO.

iv. UPON CLOSING, BUYER SHALL AUTOMATICALLY ASSUME THE RISK THAT ADVERSE MATTERS, INCLUDING BUT NOT LIMITED TO, CONSTRUCTION DEFECTS AND ADVERSE PHYSICAL AND ENVIRONMENTAL CONDITIONS, MAY NOT HAVE BEEN REVEALED BY BUYER'S INVESTIGATIONS, AND BUYER, UPON CLOSING, SHALL BE DEEMED TO HAVE WAIVED, RELINQUISHED AND RELEASED SELLER (AND SELLER'S AFFILIATES, PREDECESSORS, SUCCESSORS, PARTNERS, MEMBERS, OFFICERS, DIRECTORS, SHAREHOLDERS, TRUSTEES, EMPLOYEES, AGENTS, REPRESENTATIVES, LENDERS, CONSULTANTS AND ATTORNEYS) FROM AND AGAINST ANY AND ALL CLAIMS, DEMANDS, CAUSES OF ACTION IN LAW OR IN EQUITY (INCLUDING CAUSES OF ACTION IN TORT), LOSSES, DAMAGES, LIABILITIES, COSTS AND EXPENSES (INCLUDING REASONABLE ATTORNEYS' FEES) OF ANY AND EVERY KIND OR CHARACTER, KNOWN OR UNKNOWN, FIXED OR CONTINGENT, WHICH BUYER MIGHT HAVE ASSERTED OR ALLEGED AGAINST SELLER (AND SELLER'S AFFILIATES, PREDECESSORS, SUCCESSORS, PARTNERS, MEMBERS, OFFICERS, DIRECTORS, SHAREHOLDERS, TRUSTEES, EMPLOYEES, AGENTS, REPRESENTATIVES, LENDERS, CONSULTANTS AND ATTORNEYS) AT ANY TIME BY REASON OF OR ARISING OUT OF ANY LATENT OR PATENT CONSTRUCTION DEFECTS OR PHYSICAL CONDITIONS, VIOLATIONS OF ANY APPLICABLE LAWS AND ANY AND ALL OTHER ACTS, OMISSIONS, EVENTS, CIRCUMSTANCES OR MATTERS REGARDING THE PREMISES.

THE UNDERSIGNED ACKNOWLEDGES THAT IT HAS BEEN ADVISED BY LEGAL COUNSEL AND IS FAMILIAR WITH THE PROVISIONS OF CALIFORNIA CIVIL CODE SECTION 1542, WHICH PROVIDES AS FOLLOWS:

> "A GENERAL RELEASE DOES NOT EXTEND TO CLAIMS WHICH THE CREDITOR DOES NOT KNOW OR SUSPECT TO EXIST IN HIS OR HER FAVOR AT THE TIME OF EXECUTING THE RELEASE, WHICH IF KNOWN BY HIM OR HER MUST HAVE MATERIALLY AFFECTED HIS OR HER SETTLEMENT WITH THE DEBTOR."

THE UNDERSIGNED, BEING AWARE OF THIS CODE SECTION, HEREBY EXPRESSLY WAIVES ANY RIGHTS IT MAY HAVE THEREUNDER, AS WELL AS UNDER ANY OTHER STATUTES OR COMMON LAW PRINCIPALS OF SIMILAR EFFECT.

_____
Buyer's Initials

B. Survival of Disclaimers. The provisions of this Section 11 shall survive Closing or any termination of this Agreement.

12. **Notices.** All notices or other communications to be given by one party to the other under this Agreement shall be in writing, mailed or delivered to the other party at the following addresses:

If intended for Seller:

BMR-GAZELLE COURT LLC

Attn: Vice President, Real Estate Counsel
17190 Bernardo Center Drive
San Diego, California 92128
Phone: (858) 485-9840 Fax: (858) 485-9843

If intended for Buyer:

Isis Pharmaceuticals, Inc.
Attn: Chief Operating Officer
1896 Rutherford Road
Carlsbad, California 92008
Phone: (760) 931-9200 Fax: (760) 918-3599

with a copy to: General Counsel
Fax: 760-268-4922

Notices may be delivered by Federal Express, United Parcel Service, or other nationally recognized overnight (one-night) mail courier service, or sent by facsimile (provided a copy of such notice is deposited with an overnight courier for next business day delivery). Any such notice shall be considered given on the date of such hand or couriered delivery, confirmed facsimile transmission if received on a business day, deposit with such overnight courier for next business day delivery.

Either party may, with proper notice, at any time designate a different address to which notices shall be sent.

13. **Assignment.** Buyer may not assign its rights under this Agreement without first obtaining Seller's written approval, which approval may be given or withheld in Seller's sole discretion, *except* that Buyer may assign this agreement without Seller's approval but with written notice, to any (i) successor by merger or sale of substantially all of Buyer's assets (including, without limitation, this Agreement) in a manner such that the assignee will become liable and responsible for the performance and observance of all Buyer's duties and obligations hereunder; or (ii) corporation or other entity which controls, is controlled by, or is under common control with Buyer. In no event shall any assignment of this Agreement release or discharge Buyer from any liability or obligation hereunder unless expressly agreed otherwise by Seller in writing. Any transfer, directly or indirectly, (whether by merger, consolidation or otherwise) of any stock, partnership interest or other ownership interest in Buyer or any other transaction, in each case which results (whether directly or indirectly) in a change in control of Buyer shall constitute an assignment of this Agreement.

14. **Brokerage.** Each of Seller and Buyer represents and warrants to the other of them that it has not dealt with any broker, agent, finder or other intermediary in connection with the conveyance of the Premises or this Agreement. Each of Seller and Buyer agrees to indemnify, defend and hold the other harmless of, from and against any damages, costs, claims, losses or liabilities whatsoever (including attorney's fees, expenses and court costs) arising from any breach by the indemnifying party of the foregoing warranties, representations and agreements. This Section shall survive Closing under this Agreement.

15. **Time of the Essence.** Time, wherever mentioned herein, shall be of the essence of this Agreement.

16. **Binding Effect.** This Agreement shall be binding upon and inure to the benefit of Seller and Buyer and their respective successors, heirs and assigns.

17. **Entire Agreement.** This Agreement constitutes the entire agreement between the parties hereto regarding the transaction contemplated hereby and there are no other terms, covenants, conditions, warranties, representations or statements, oral or otherwise, of any kind whatsoever. Any agreement hereafter made shall be ineffective to change, modify, discharge or effect an abandonment of this Agreement in whole or in part unless such agreement is in writing and signed by the party against whom enforcement of the change, modification, discharge or abandonment is sought.

18. **Headings.** The headings incorporated in this Agreement are for convenience and reference only and are not a part of this Agreement and do not in any way control, define, limit, or add to the terms and conditions hereof.

19. **Governing Law.** This Agreement shall be construed, interpreted and governed by the laws of the State of California.

20. **Counterparts.** This Agreement may be executed in any number of counterparts, each of which shall be an original, and such counterparts together shall constitute one and the same instrument.

21. **Attorneys' Fees.** If either party commences an action against the other party arising out of or in connection with this Agreement, then the prevailing party shall be entitled to have and recover from the other party reasonable attorneys' fees, charges and disbursements and costs of suit in proportion to [***] up to a maximum of 100%; provided, however, that in the case where the prevailing party is awarded any equitable relief, then the prevailing party may recover the full amount of such costs and attorney's fees. For example, if the prevailing party [***] and no equitable relief, but [***], and the prevailing party had two hundred thousand dollars ($200,000) in costs and attorneys' fees, then such prevailing party would be entitled to recover [***] of such costs and attorneys' fees.

[REMAINDER OF PAGE INTENTIONALLY LEFT BLANK]

IN WITNESS WHEREOF, the parties hereto have duly executed this Agreement, under seal, as of the day and year first-above written.

SELLER:
BMR-GAZELLE COURT LLC,
a Delaware limited liability company,

By: _____
Name: _____
Title: _____

BUYER:
ISIS PHARMACEUTICALS, INC.,
a Delaware corporation,

By: _____
Name: _____
Title: _____

ACKNOWLEDGMENT AND CONSENT OF TITLE COMPANY

On this day of , 20 , the undersigned, the Title Company named in the foregoing Agreement, intending to be legally bound hereby, agrees to keep, observe and perform the terms and conditions of said Agreement relating to the holding and disbursement of the Deposit (as defined in the Agreement), together with any interest earned thereon, and all additional monies paid to it in escrow pursuant to the terms and conditions thereof. Title Company shall not incur any liability to anyone for damages, losses, or expenses except for fraud, negligence or willful conversation in respect to any action taken or omitted in good faith. Title Company may tender into the registry of any court of competent jurisdiction any escrow funds if it deems that there is a dispute with respect to the disbursement of such funds. Thereafter, Title Company will be discharged from all further duties and liabilities hereunder.

TITLE COMPANY:

[ ]

By: _____

EXHIBIT "A"
(Legal Description of Premises)

PARCEL 1:

PARCEL "A" OF CERTIFICATE OF COMPLIANCE NO. ADJ 09-05 RECORDED JANUARY 19, 2010 AS INSTRUMENT NO. 2010-0024854 OF OFFICIAL RECORDS, DESCRIBED AS FOLLOWS:

LOT 14 OF CARLSBAD TRACT NO. 97-13-02, ACCORDING TO MAP THEREOF NO. 15505, IN THE CITY OF CARLSBAD, COUNTY OF SAN DIEGO, STATE OF CALIFORNIA, RECORDED IN THE OFFICE OF THE COUNTY RECORDER OF SAN DIEGO COUNTY ON JANUARY 23, 2007 AS FILE NO. 2007-0047588, TOGETHER WITH A PORTION OF LOT 'B' OF RANCHO AGUA HEDIONDA, IN THE CITY OF CARLSBAD, COUNTY OF SAN DIEGO, STATE OF CALIFORNIA, ACCORDING TO MAP THEREOF NO. 823, FILED IN THE OFFICE OF THE COUNTY RECORDER OF SAN DIEGO COUNTY, NOVEMBER 16, 1896, BEING MORE PARTICULARLY DESCRIBED AS FOLLOWS:

BEGINNING AT THE NORTHWEST CORNER OF SAID LOT 14; THENCE, ALONG THE NORTH LINE OF SAID LOT 14, NORTH 89°09'41" EAST 629.31 FEET; THENCE SOUTH 00°31'59" WEST 8.11 FEET; THENCE NORTH 89°53'58" EAST 392.46 FEET; THENCE NORTH 53°13'30" EAST 15.15 FEET; THENCE SOUTH 56°49'30" EAST 85.95 FEET TO THE NORTHEAST CORNER OF SAID LOT 14, SAID CORNER BEING ON A NON-TANGENT 264.00 FOOT RADIUS CURVE CONCAVE NORTHWESTERLY, THE RADIAL LINE TO SAID POINT BEARS SOUTH 56°49'30" EAST; THENCE, ALONG THE EAST LINE OF SAID LOT 14, SOUTHWESTERLY ALONG SAID CURVE THROUGH A CENTRAL ANGLE OF 5°50'08" AN ARC DISTANCE OF DISTANCE OF 26.89; THENCE, TANGENT TO SAID CURVE, SOUTH 39°00'38" WEST 329.54 FEET TO THE BEGINNING OF A TANGENT 736.00 FOOT RADIUS CURVE CONCAVE SOUTHEASTERLY; THENCE SOUTHWESTERLY ALONG SAID CURVE THROUGH A CENTRAL ANGLE OF 25°07'33" A DISTANCE OF 322.76 TO THE SOUTHEAST CORNER OF SAID LOT 14, SAID CORNER ALSO BEING A POINT ON THE SUBDIVISION BOUNDARY OF MAP NO. 14926; THENCE, ALONG THE SOUTH LINE OF SAID LOT 14 AND THE BOUNDARY OF SAID MAP NO. 14926, NON-TANGENT TO SAID CURVE NORTH 52°33'23" WEST 148.70 FEET; THENCE SOUTH 48°06'30" WEST, 21.89 FEET TO THE BEGINNING OF A 100.00 FOOT RADIUS CURVE CONCAVE NORTHWESTERLY; THENCE SOUTHWESTERLY ALONG SAID CURVE THROUGH A CENTRAL ANGLE OF 34°22'48" AN ARC DISTANCE OF 60.00 FEET; THENCE 82°29'18" WEST 147.20 FEET; THENCE NORTH 89°14'55" WEST 410.06 FEET TO THE SOUTHWEST CORNER OF SAID LOT 14; THENCE, LEAVING SAID LOT 14 AND CONTINUING ALONG THE BOUNDARY OF SAID MAP NO. 14926, SOUTH 29°36'38" WEST 51.14 FEET; THENCE NORTH 77°38'20" WEST 216.59 FEET; THENCE, LEAVING THE BOUNDARY OF SAID MAP NO. 14926, NORTH 43°05'58" EAST 78.45 FEET; THENCE NORTH 01°47'45" EAST 442.55 FEET TO A POINT ON THE SOUTHERLY BOUNDARY OF THAT PUBLIC

STREET AND UTILITY EASEMENT RECORDED JANUARY 23, 2007 AS FILE NO. 2007-0047586, SAID POINT BEING ON A NON-TANGENT 836.00 FOOT RADIUS CURVE CONCAVE NORTHERLY, A RADIAL LINE TO SAID POINT BEARS SOUTH 23°00'29" WEST; THENCE, EASTERLY ALONG SAID EASEMENT AND SAID CURVE, THROUGH A CENTRAL ANGLE OF 10°54'11" AN ARC DISTANCE OF 159.09 TO THE BEGINNING OF A COMPOUND 56.00 FOOT RADIUS CURVE CONCAVE WESTERLY; THENCE NORTHERLY ALONG SAID CURVE THROUGH A CENTRAL ANGLE OF 181°26'49" AN ARC DISTANCE OF 177.34 TO THE POINT OF BEGINNING.

PARCEL 2:

AN EASEMENT FOR A PRIVATE DRAINAGE OVER AND ACROSS LOT 4 OF CARLSBAD TRACT NO. 97-13-01, CARLSBAD OAKS NORTH PHASE 1, IN THE CITY OF CARLSBAD, COUNTY OF SAN DIEGO, STATE OF CALIFORNIA, ACCORDING TO MAP THEREOF NO. 14926, RECORDED IN THE OFFICE OF THE COUNTY RECORDER OF SAN DIEGO COUNTY ON DECEMBER 15, 2004, AS CREATED BY EASEMENT AGREEMENT EXECUTED BY KILROY REALTY FINANCE PARTNERSHIP, L.P., A DELAWARE LIMITED PARTNERSHIP, TECHBILT CONSTRUCTION CORP., A CALIFORNIA CORPORATION AND CARLSBAD OAKS NORTH PARTNERS, L.P., A CALIFORNIA LIMITED PARTNERSHIP, DATED JANUARY 20, 2010 AND RECORDED JANUARY 29, 2010 AS INSTRUMENT NO. 2010-0047608 OF OFFICIAL RECORDS.

APN: 209-120-11 and a portion of 209-120-17

EXHIBIT "B"

FORM OF DEED

RECORDING REQUESTED BY
AND WHEN RECORDED MAIL TO:

The undersigned Grantor declares: documentary transfer tax not shown pursuant to Section 11932 of the Revenue and Taxation Code, as amended

GRANT DEED

FOR VALUE RECEIVED, BMR-GAZELLE COURT LLC, a Delaware limited partnership ("**Grantor**"), grants to ISIS PHARMACEUTICALS, INC., a Delaware corporation ("Grantee"), all that certain real property (the "**Property**") situated in the City of Carlsbad, County of San Diego, State of California, described on Exhibit A attached hereto and by this reference incorporated herein, subject to all covenants, conditions, easements, encumbrances and all other matters affecting the Property.

IN WITNESS WHEREOF, the undersigned has executed this Grant Deed dated as of , 20 .

BMR-GAZELLE COURT LLC,
a Delaware limited liability company

By: _____
Name: _____
Title: _____

STATE OF CALIFORNIA }
COUNTY OF } *S.S.*

On , before me, , a Notary Public in and for said County and State, personally appeared, ; , who proved to me on the basis of satisfactory evidence to be the person(s) whose name(s) is/are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity(ies), and that by his/her/their signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

I certify under PENALTY OF PERJURY under the laws of the State of California that the foregoing paragraph is true and correct.

WITNESS my hand and official seal.

Signature: _____

(Notary Seal)

EXHIBIT A TO FORM OF DEED

DESCRIPTION OF PROPERTY

PARCEL 1:

PARCEL "A" OF CERTIFICATE OF COMPLIANCE NO. ADJ 09-05 RECORDED JANUARY 19, 2010 AS INSTRUMENT NO. 2010-0024854 OF OFFICIAL RECORDS, DESCRIBED AS FOLLOWS:

LOT 14 OF CARLSBAD TRACT NO. 97-13-02, ACCORDING TO MAP THEREOF NO. 15505, IN THE CITY OF CARLSBAD, COUNTY OF SAN DIEGO, STATE OF CALIFORNIA, RECORDED IN THE OFFICE OF THE COUNTY RECORDER OF SAN DIEGO COUNTY ON JANUARY 23, 2007 AS FILE NO. 2007-0047588, TOGETHER WITH A PORTION OF LOT 'B' OF RANCHO AGUA HEDIONDA, IN THE CITY OF CARLSBAD, COUNTY OF SAN DIEGO, STATE OF CALIFORNIA, ACCORDING TO MAP THEREOF NO. 823, FILED IN THE OFFICE OF THE COUNTY RECORDER OF SAN DIEGO COUNTY, NOVEMBER 16, 1896, BEING MORE PARTICULARLY DESCRIBED AS FOLLOWS:

BEGINNING AT THE NORTHWEST CORNER OF SAID LOT 14; THENCE, ALONG THE NORTH LINE OF SAID LOT 14, NORTH 89°09'41" EAST 629.31 FEET; THENCE SOUTH 00°31'59" WEST 8.11 FEET; THENCE NORTH 89°53'58" EAST 392.46 FEET; THENCE NORTH 53°13'30" EAST 15.15 FEET; THENCE SOUTH 56°49'30" EAST 85.95 FEET TO THE NORTHEAST CORNER OF SAID LOT 14, SAID CORNER BEING ON A NON-TANGENT 264.00 FOOT RADIUS CURVE CONCAVE NORTHWESTERLY, THE RADIAL LINE TO SAID POINT BEARS SOUTH 56°49'30" EAST; THENCE, ALONG THE EAST LINE OF SAID LOT 14, SOUTHWESTERLY ALONG SAID CURVE THROUGH A CENTRAL ANGLE OF 5°50'08" AN ARC DISTANCE OF DISTANCE OF 26.89; THENCE, TANGENT TO SAID CURVE, SOUTH 39°00'38" WEST 329.54 FEET TO THE BEGINNING OF A TANGENT 736.00 FOOT RADIUS CURVE CONCAVE SOUTHEASTERLY; THENCE SOUTHWESTERLY ALONG SAID CURVE THROUGH A CENTRAL ANGLE OF 25°07'33" A DISTANCE OF 322.76 TO THE SOUTHEAST CORNER OF SAID LOT 14, SAID CORNER ALSO BEING A POINT ON THE SUBDIVISION BOUNDARY OF MAP NO. 14926; THENCE, ALONG THE SOUTH LINE OF SAID LOT 14 AND THE BOUNDARY OF SAID MAP NO. 14926, NON-TANGENT TO SAID CURVE NORTH 52°33'23" WEST 148.70 FEET; THENCE SOUTH 48°06'30" WEST, 21.89 FEET TO THE BEGINNING OF A 100.00 FOOT RADIUS CURVE CONCAVE NORTHWESTERLY; THENCE SOUTHWESTERLY ALONG SAID CURVE THROUGH A CENTRAL ANGLE OF 34°22'48" AN ARC DISTANCE OF 60.00 FEET; THENCE 82°29'18" WEST 147.20 FEET; THENCE NORTH 89°14'55" WEST 410.06 FEET TO THE SOUTHWEST CORNER OF SAID LOT 14; THENCE, LEAVING SAID LOT 14 AND CONTINUING ALONG THE BOUNDARY OF SAID MAP NO. 14926, SOUTH 29°36'38" WEST 51.14 FEET; THENCE NORTH 77°38'20" WEST 216.59 FEET; THENCE, LEAVING THE BOUNDARY OF SAID MAP NO. 14926, NORTH 43°05'58" EAST 78.45 FEET; THENCE NORTH 01°47'45" EAST

442.55 FEET TO A POINT ON THE SOUTHERLY BOUNDARY OF THAT PUBLIC STREET AND UTILITY EASEMENT RECORDED JANUARY 23, 2007 AS FILE NO. 2007-0047586, SAID POINT BEING ON A NON-TANGENT 836.00 FOOT RADIUS CURVE CONCAVE NORTHERLY, A RADIAL LINE TO SAID POINT BEARS SOUTH 23°00'29" WEST; THENCE, EASTERLY ALONG SAID EASEMENT AND SAID CURVE, THROUGH A CENTRAL ANGLE OF 10°54'11" AN ARC DISTANCE OF 159.09 TO THE BEGINNING OF A COMPOUND 56.00 FOOT RADIUS CURVE CONCAVE WESTERLY; THENCE NORTHERLY ALONG SAID CURVE THROUGH A CENTRAL ANGLE OF 181°26'49" AN ARC DISTANCE OF 177.34 TO THE POINT OF BEGINNING.

PARCEL 2:

AN EASEMENT FOR A PRIVATE DRAINAGE OVER AND ACROSS LOT 4 OF CARLSBAD TRACT NO. 97-13-01, CARLSBAD OAKS NORTH PHASE 1, IN THE CITY OF CARLSBAD, COUNTY OF SAN DIEGO, STATE OF CALIFORNIA, ACCORDING TO MAP THEREOF NO. 14926, RECORDED IN THE OFFICE OF THE COUNTY RECORDER OF SAN DIEGO COUNTY ON DECEMBER 15, 2004, AS CREATED BY EASEMENT AGREEMENT EXECUTED BY KILROY REALTY FINANCE PARTNERSHIP, L.P., A DELAWARE LIMITED PARTNERSHIP, TECHBILT CONSTRUCTION CORP., A CALIFORNIA CORPORATION AND CARLSBAD OAKS NORTH PARTNERS, L.P., A CALIFORNIA LIMITED PARTNERSHIP, DATED JANUARY 20, 2010 AND RECORDED JANUARY 29, 2010 AS INSTRUMENT NO. 2010-0047608 OF OFFICIAL RECORDS.

APN: 209-120-11 and a portion of 209-120-17

EXHIBIT "C"
(Bill of Sale and Assignment and Assumption of Warranties)

THIS BILL OF SALE AND ASSIGNMENT AND ASSUMPTION OF WARRANTIES (the "Assignment") made as of this [ ] day of , 20 between BMR-GAZELLE COURT LLC, a Delaware limited liability company (the "Assignor"), and ISIS PHARMACEUTICALS, INC., a Delaware corporation ("Assignee"). Assignor and Assignee are parties to the Agreement of Purchase and Sale dated , between Assignor and Assignee (the "Agreement"). Capitalized terms used herein but not otherwise defined shall have the meanings ascribed thereto in the Agreement.

1. Assignor is the owner of that certain real property located in Carlsbad, California, more particularly described in Exhibit A attached hereto (the "Real Property"). Assignor hereby assigns, transfers, sets over and conveys to Assignee all of Assignor's right, title and interest, in, to, and under the following, in each case to the extent assignable without payment or fee: all warranties, indemnities, guaranties (express or implied), applications, permits, authorizations, approvals and licenses (to the extent applicable in any way to the above referenced Real Property and any improvements thereon (collectively, the **"**Warranties**"**).

2. Assignee does hereby assume and agree to perform all of Assignor's obligations under the Warranties accruing from and after the date hereof. Assignee agrees to indemnify, protect, defend and hold Assignor harmless from and against any and all liabilities, losses, costs, damages and expenses (including reasonable attorneys' fees) directly or indirectly arising out of or related to any breach or default in Assignee's obligations hereunder.

3. Sale of Personalty. For good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, Assignor hereby sells, transfers, sets over and conveys to Assignee the following:

(a) Tangible Personal Property. All right, title and interest of Assignor in and to all all tangible personal property now or hereafter located on, or used exclusively in connection with, the operation, ownership, maintenance, occupancy or improvement of the Land (collectively, the **"**Tangible Personal Property**"**; and

(b) Intangible Property. The following property to the extent assignable: All, right, title and interest of Assignor, if any, in and to all intangible personal property now or hereafter used exclusively in connection with the operation, ownership, maintenance, management, or occupancy of the Real Property (to the extent assignable); the plans and specifications for the Improvements (to the extent assignable); insurance proceeds received by (or owed to) Seller which relate to damage to the Land or Improvements caused by a casualty that has occurred prior to the Closing Date and for which restoration has not previously occurred, but only to the extent that such proceeds have not been applied by Seller prior to the Closing Date towards the cost of (a) pursuit or settlement of the applicable insurance claim, (b) the clearing of debris or other expenses associated with securing the Land or Improvements, or (c) restoration of the Land or Improvements; and condemnation awards or claims thereto.

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4. This Assignment shall be binding upon and inure to the benefit of Assignor and Assignee and their respective heirs, executors, administrators, successors and assigns.

5. This Assignment may be executed in two or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument.

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IN WITNESS WHEREOF, Assignor and Assignee have each executed this Assignment as of the date first written above.

ASSIGNOR:

BMR-2600 GAZELLE COURT LLC,
a Delaware limited liability company

By: _____
Name: _____
Title: _____

ASSIGNEE:

ISIS PHARMACEUTICALS, INC.,
a Delaware corporation

By: _____
Name: _____
Title: _____

EXHIBIT A TO FORM OF ASSIGNMENT AND ASSUMPTION OF WARRANTIES

DESCRIPTION OF PREMISES

PARCEL 1:

PARCEL “A” OF CERTIFICATE OF COMPLIANCE NO. ADJ 09-05 RECORDED JANUARY 19, 2010 AS INSTRUMENT NO. 2010-0024854 OF OFFICIAL RECORDS, DESCRIBED AS FOLLOWS:

LOT 14 OF CARLSBAD TRACT NO. 97-13-02, ACCORDING TO MAP THEREOF NO. 15505, IN THE CITY OF CARLSBAD, COUNTY OF SAN DIEGO, STATE OF CALIFORNIA, RECORDED IN THE OFFICE OF THE COUNTY RECORDER OF SAN DIEGO COUNTY ON JANUARY 23, 2007 AS FILE NO. 2007-0047588, TOGETHER WITH A PORTION OF LOT ‘B’ OF RANCHO AGUA HEDIONDA, IN THE CITY OF CARLSBAD, COUNTY OF SAN DIEGO, STATE OF CALIFORNIA, ACCORDING TO MAP THEREOF NO. 823, FILED IN THE OFFICE OF THE COUNTY RECORDER OF SAN DIEGO COUNTY, NOVEMBER 16, 1896, BEING MORE PARTICULARLY DESCRIBED AS FOLLOWS:

BEGINNING AT THE NORTHWEST CORNER OF SAID LOT 14; THENCE, ALONG THE NORTH LINE OF SAID LOT 14, NORTH 89°09'41" EAST 629.31 FEET; THENCE SOUTH 00°31'59" WEST 8.11 FEET; THENCE NORTH 89°53'58" EAST 392.46 FEET; THENCE NORTH 53°13'30" EAST 15.15 FEET; THENCE SOUTH 56°49'30" EAST 85.95 FEET TO THE NORTHEAST CORNER OF SAID LOT 14, SAID CORNER BEING ON A NON-TANGENT 264.00 FOOT RADIUS CURVE CONCAVE NORTHWESTERLY, THE RADIAL LINE TO SAID POINT BEARS SOUTH 56°49'30" EAST; THENCE, ALONG THE EAST LINE OF SAID LOT 14, SOUTHWESTERLY ALONG SAID CURVE THROUGH A CENTRAL ANGLE OF 5°50'08" AN ARC DISTANCE OF DISTANCE OF 26.89; THENCE, TANGENT TO SAID CURVE, SOUTH 39°00'38" WEST 329.54 FEET TO THE BEGINNING OF A TANGENT 736.00 FOOT RADIUS CURVE CONCAVE SOUTHEASTERLY; THENCE SOUTHWESTERLY ALONG SAID CURVE THROUGH A CENTRAL ANGLE OF 25°07'33" A DISTANCE OF 322.76 TO THE SOUTHEAST CORNER OF SAID LOT 14, SAID CORNER ALSO BEING A POINT ON THE SUBDIVISION BOUNDARY OF MAP NO. 14926; THENCE, ALONG THE SOUTH LINE OF SAID LOT 14 AND THE BOUNDARY OF SAID MAP NO. 14926, NON-TANGENT TO SAID CURVE NORTH 52°33'23" WEST 148.70 FEET; THENCE SOUTH 48°06'30" WEST, 21.89 FEET TO THE BEGINNING OF A 100.00 FOOT RADIUS CURVE CONCAVE NORTHWESTERLY; THENCE SOUTHWESTERLY ALONG SAID CURVE THROUGH A CENTRAL ANGLE OF 34°22'48" AN ARC DISTANCE OF 60.00 FEET; THENCE 82°29'18" WEST 147.20 FEET; THENCE NORTH 89°14'55" WEST 410.06 FEET TO THE SOUTHWEST CORNER OF SAID LOT 14; THENCE, LEAVING SAID LOT 14 AND CONTINUING ALONG THE BOUNDARY OF SAID MAP NO. 14926, SOUTH 29°36'38" WEST

51.14 FEET; THENCE NORTH 77°38'20" WEST 216.59 FEET; THENCE, LEAVING THE BOUNDARY OF SAID MAP NO. 14926, NORTH 43°05'58" EAST 78.45 FEET; THENCE NORTH 01°47'45" EAST 442.55 FEET TO A POINT ON THE SOUTHERLY BOUNDARY OF THAT PUBLIC STREET AND UTILITY EASEMENT RECORDED JANUARY 23, 2007 AS FILE NO. 2007-0047586, SAID POINT BEING ON A NON-TANGENT 836.00 FOOT

RADIUS CURVE CONCAVE NORTHERLY, A RADIAL LINE TO SAID POINT BEARS SOUTH 23°00'29" WEST; THENCE, EASTERLY ALONG SAID EASEMENT AND SAID CURVE, THROUGH A CENTRAL ANGLE OF 10°54'11" AN ARC DISTANCE OF 159.09 TO THE BEGINNING OF A COMPOUND 56.00 FOOT RADIUS CURVE CONCAVE WESTERLY; THENCE NORTHERLY ALONG SAID CURVE THROUGH A CENTRAL ANGLE OF 181°26'49" AN ARC DISTANCE OF 177.34 TO THE POINT OF BEGINNING.

PARCEL 2:

AN EASEMENT FOR A PRIVATE DRAINAGE OVER AND ACROSS LOT 4 OF CARLSBAD TRACT NO. 97-13-01, CARLSBAD OAKS NORTH PHASE 1, IN THE CITY OF CARLSBAD, COUNTY OF SAN DIEGO, STATE OF CALIFORNIA, ACCORDING TO MAP THEREOF NO. 14926, RECORDED IN THE OFFICE OF THE COUNTY RECORDER OF SAN DIEGO COUNTY ON DECEMBER 15, 2004, AS CREATED BY EASEMENT AGREEMENT EXECUTED BY KILROY REALTY FINANCE PARTNERSHIP, L.P., A DELAWARE LIMITED PARTNERSHIP, TECHBILT CONSTRUCTION CORP., A CALIFORNIA CORPORATION AND CARLSBAD OAKS NORTH PARTNERS, L.P., A CALIFORNIA LIMITED PARTNERSHIP, DATED JANUARY 20, 2010 AND RECORDED JANUARY 29, 2010 AS INSTRUMENT NO. 2010-0047608 OF OFFICIAL RECORDS.

APN: 209-120-11 and a portion of 209-120-17

EXHIBIT "D"
LEASE TERMINATION AGREEMENT

THIS TERMINATION AGREEMENT (this "Agreement") is entered into as of , 20[ ], by and between BMR-GAZELLE COURT LLC, a Delaware limited liability company ("Landlord"), and ISIS PHARMACEUTICALS, INC., a Delaware corporation ("Tenant" and, together with Landlord, the "Parties").

RECITALS:

A. The Parties entered into that certain Lease Agreement, dated as of March 30, 2010 (the "Lease"). All capitalized terms used and not otherwise defined herein shall have the meanings ascribed thereto in the Lease.

B. The Parties now wish to terminate the Lease on the terms and conditions set forth herein.

NOW, THEREFORE, the Parties to this Agreement hereby agree as follows:

1. Termination of the Lease. Effective as of , 20 (the "Effective Date"), the Lease is terminated by consent of the Parties; provided, however, that such termination shall not terminate or limit the effect of those provisions of the Lease which by their terms survive expiration or termination of the Lease.

2. Entire Agreement. This Agreement shall constitute the final, complete and exclusive expression of the intentions of the Parties hereto with respect to the subject matter hereof and shall supersede all previous communications, representations, agreements, promises or statements, either oral or written, by or between any Party with regard to the subject matter hereof.

3. Counterparts. This Agreement may be executed in one or more counterparts, each of which shall be read together and be construed as one instrument. A facsimile or other electronic copy of a signature shall be as binding as an original signature.

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IN WITNESS WHEREOF, the parties have executed and delivered this Agreement as of the Effective Date.

LANDLORD:

BMR-2600 GAZELLE COURT LLC,
a Delaware limited liability company

By: _____
Name: _____
Title: _____

TENANT:

ISIS PHARMACEUTICALS, INC.,
a Delaware corporation

By: _____
Name: _____
Title: _____

EXHIBIT "E"
(FIRPTA Affidavit)

CERTIFICATE REGARDING FOREIGN INVESTMENT IN REAL PROPERTY TAX ACT (ENTITY TRANSFEROR)

Section 1445 of the Internal Revenue Code provides that a transferee (purchaser) of a U.S. real property interest must withhold tax if the transferor (seller) is a foreign person. To inform the transferee (purchaser) that withholding tax is not required upon the disposition of a U.S. real property interest by BMR-GAZELLE COURT LLC, a Delaware limited liability company ("Transferor"). Transferor hereby certifies:

1. Transferor is not a foreign corporation, foreign partnership, foreign trust, or foreign estate (as those terms are defined in the Internal Revenue Code and Income Tax Regulations).

2. Transferor's Federal Employer Identification Number is .

3. Transferor's office address is:

17190 Bernardo Center Drive
San Diego, CA 92128

4. The address or description of the property which is the subject matter of the disposition is , Carlsbad, California.

Transferor understands that this certification must be disclosed to the Internal Revenue Service by transferee and that any false statement contained herein could be punished by fine, imprisonment, or both.

Transferor declares that it has examined this certification and to the best of its knowledge and belief, it is true, correct and complete, and further declares that the individual executing this certification on behalf of Transferor has full authority to do so.

BMR-2600 GAZELLE COURT LLC,
a Delaware limited liability company

By: _____
Name: _____
Title: _____

EXHIBIT "F"
(Permitted Exceptions)

1. General and special taxes and assessments for the fiscal year 2010-2011, a lien not yet due or payable.

2. The lien of special tax assessed pursuant to Chapter 2.5 commencing with Section 53311 of the California Government Code for Community Facilities District No. 1, as disclosed by Notice of Special Tax Lien recorded June 29, 2004 as Instrument No. 2004-0606773 of Official Records.

3. The lien of special tax assessed pursuant to Chapter 2.5 commencing with Section 53311 of the California Government Code for Community Facilities District No. 3, as disclosed by that certain Amendment to the Notice of Special Tax Lien recorded November 17, 2005 as Instrument No. 2005-0998004 of Official Records.

4. The lien of supplemental taxes, if any, assessed pursuant to Chapter 3.5 commencing with Section 75 of the California Revenue and Taxation Code, none currently due or payable.

5. The terms and provisions contained in the document entitled "Notice of Restriction on Real Property" recorded November 9, 2004 as Instrument No. 2004-1066056 of Official Records.

6. The terms and provisions contained in the document entitled "Notice of Waiver Concerning Proximity of the Planned or Existing Palomar Airport Road and Melrose Drive Transportation Corridors Case No: CT 97-13" recorded November 9, 2004 as Instrument No. 2004-1066058 of Official Records.

7. The terms and provisions contained in the document entitled "Hold Harmless Agreement Drainage" recorded December 15, 2004 as Instrument No. 2004-1180067 of Official Records.

8. The terms and provisions contained in the document entitled "Waiver and Consent to Creation of a Community Facilities District and Agreement to Pay Fair Share Cost of CT 97-13 ("Agreement")" recorded December 15, 2004 as Instrument No. 2004-1180069 of Official Records; as modified by the terms and provisions contained in the document entitled "Amendment No. 1 to Waiver and Consent to Creation of the Community Facilities District (CT 97-13), Carlsbad Oaks North Partners, L.P." recorded November 4, 2005 as Instrument No. 2005-0964619 of Official Records.

9. The terms and provisions contained in the document entitled "Agreement between Developer/Owner and the City of Carlsbad for the Payment of a Local Drainage Area Fee" recorded December 21, 2004 as Instrument No. 2004-1201221 of Official Records.

10. The terms and provisions contained in the document entitled “Hold Harmless Agreement Drainage” recorded December 1, 2006 as Instrument No. 2006-0854466 of Official Records.

11. The terms and provisions contained in the document entitled “Hold Harmless Agreement Geological Failure” recorded December 1, 2006 as Instrument No. 2006-0854467 of Official Records.

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12. Abutter’s rights of ingress and egress to or from Whiptail Loop, except access opening, have been dedicated or relinquished on Map No. 15505 as referred to in the legal description.

13. An easement shown or dedicated on Map No. 15505 as referred to in the legal description

For: Sight distance corridor and incidental purposes.

14. A Recital as shown on Map No. 15505 as follows:

1. No structure, fence, wall, tree, shrub, sign or other object over 30 inches above the street level may be placed or permitted to encroach within the area identified as a sight distance corridor in accordance with City standard public street-design criteria, Section 8.B.3. The underlying property owner shall maintain this condition.

2. Geotechnical Caution:

The owner of the property on behalf of itself and all of its successors in interest has agreed to hold harmless and indemnify the City of Carlsbad from any action that may arise through any geotechnical failure, ground water separate or land subsidence and subsequent damage that may occur, or adjacent to, this subdivision due to its construction, operation or maintenance.

15. Covenants, conditions, restrictions, easements, assessments, liens, charges, terms and provisions in the document recorded February 5, 2007 as Instrument No. 2007-0081082 of Official Records, which provide that a violation thereof shall not defeat or render invalid the lien of any first mortgage or deed of trust made in good faith and for value, but deleting any covenant, condition, or restriction indicating a preference, limitation or discrimination based on race, color, religion, sex, sexual orientation, marital status, ancestry, disability, handicap, familial status, national origin or source of income (as defined in California Government Code §12955(p)), to the extent such covenants, conditions or restrictions violate 42 U.S.C. §3604(c) or California Government Code §12955. Lawful restrictions under state and federal law on the age of occupants in senior housing or housing for older persons shall not be construed as restrictions based on familial status.

16. An easement for public utilities and incidental purposes, recorded March 7, 2008 as Instrument No. 2008-0122770 of Official Records.
In Favor of: San Diego Gas & Electric Company, a Corporation
Affects: The land

17. An easement for public utilities and incidental purposes, recorded March 7, 2008 as Instrument No. 2008-0122771 of Official Records.
In Favor of: San Diego Gas & Electric Company, a Corporation
Affects: The land

18. The terms and provisions contained in the document entitled Memorandum of Repurchase Rights in favor of Techbilt Construction Corp., a California corporation recorded March 03, 2010 as Instrument no. 2010-0104273 of Official Records.

19. The following matters disclosed by an ALTA/ACSM survey made by O’Day Consultants on February 2010, designated Job No. 091278-01:

Storm Drain, HDPE Storm Drain, Catch Basin & Spillway, Desiltation Basin, CMP Riser, Concrete Anchors, Subdrains, Irrigation Control Pedestral, Irrigation Control Valves/Boxes, PVC Riser, Brow Ditc, Cleanout and Water Meters.

EXHIBIT H
ACKNOWLEDGEMENT OF TERM COMMENCEMENT DATE
AND TERM EXPIRATION DATE

THIS ACKNOWLEDGEMENT OF TERM COMMENCEMENT DATE AND TERM EXPIRATION DATE is entered into as of [ ], 20[ ], with reference to that certain Lease (the “Lease”) dated as of March [ ], 2010, by ISIS PHARMACEUTICALS, INC., a Delaware corporation (“Tenant”), in favor of BMR-GAZELLE COURT LLC, a Delaware limited liability company (“Landlord”). All capitalized terms used herein without definition shall have the meanings ascribed to them in the Lease.

Tenant hereby confirms the following:

1. Tenant accepted possession of the Premises on [ ], 20[ ].

2. The Premises are in good order, condition and repair.

3. The Building Improvements required to be constructed by Landlord under the Lease have been Substantially Completed, subject to the Punchlist Items.

4. Subject to Landlord's completion of the Punchlist Items, all conditions of the Lease to be performed by Landlord as a condition to the full effectiveness of the Lease have been satisfied, and Landlord has fulfilled all of its duties in the nature of inducements offered to Tenant where the fulfillment of such duties was a condition to the full effectiveness of the Lease.

5. In accordance with the provisions of Section 2.2 of the Lease, the Term Commencement Date is [ ], 20[ ], and, unless the Lease is terminated prior to the Term Expiration Date pursuant to its terms, the Term Expiration Date shall be [ ], 20[ ].

6. Tenant commenced occupancy of the Premises for the Permitted Use on [ ], 20[ ].

7. The Lease is in full force and effect, and the same represents the entire agreement between Landlord and Tenant concerning the Premises[, except [ ]].

8. Tenant has no existing defenses against the enforcement of the Lease by Landlord, and there exist no offsets or credits against Rent owed or to be owed by Tenant.

9. The undersigned Tenant has not made any prior assignment, transfer, hypothecation or pledge of the Lease or of the rents thereunder or sublease of the Premises or any portion thereof.

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IN WITNESS WHEREOF, Tenant has executed this Acknowledgment of Term Commencement Date and Term Expiration Date as of the date first written above.

TENANT:

ISIS PHARMACEUTICALS, INC.,
a Delaware corporation

By: _____
Name: _____
Title: _____

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R §§ 200.80(b)4, AND 240.24b-2

EXECUTION COPY

SECOND AMENDMENT TO LEASE AGREEMENT

THIS SECOND AMENDMENT TO LEASE AGREEMENT (this "***Amendment***") is entered into as of this 30th day of March, 2010 (the "***Effective Date***"), by and between BMR-2282 FARADAY AVENUE LLC, a Delaware limited liability company ("***Landlord***"), and ISIS PHARMACEUTICALS, INC., a Delaware corporation ("***Tenant***").

RECITALS

A. WHEREAS, Landlord and Tenant entered into that certain Lease dated as of September 19, 2005, as amended by that certain First Amendment to Lease Agreement dated as of May 8, 2007 (such Lease, as so amended, the "***Lease***"), whereby Tenant leases from Landlord certain premises located at 2282 Faraday Avenue in Carlsbad, California, as more particularly described in the Lease ((the "***Premises***").

B. WHEREAS, Landlord and Tenant desire to extend the Lease Term and provide Tenant with certain purchase options with respect to the Premises, all as more particularly described herein; and

C. WHEREAS, Landlord and Tenant desire to modify and amend the Lease only in the respects and on the conditions hereinafter stated.

AGREEMENT

NOW, THEREFORE, Landlord and Tenant, in consideration of the mutual promises contained herein and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, and intending to be legally bound, agree as follows:

1. Definitions. For purposes of this Amendment, capitalized terms shall have the meanings ascribed to them in the Lease unless otherwise defined herein.

2. Lease Term Extension. Section 2.1 of the Lease is hereby replaced in its entirety with the following:

"Lease Term. The term of this Lease shall commence on September 19, 2005 (the "***Commencement Date***") and end on December 31, 2031 (the "***Lease Term***"), subject to earlier termination of this Lease as provided herein; provided, however, that Tenant shall have four (4) options to extend the Lease Term, as further described in Article 36."

3. Tenant's Purchase Option. Article 24 of the Lease is hereby amended by adding the following Section 24.3:

"24.3 Purchase Option.

24.3.1 Tenant is hereby granted seven separate options to purchase the Premises from Landlord on the dates set forth in Section 24.2.1 of that certain Lease Agreement dated as of March 30, 2010 by and between BMR-Gazelle Court LLC, as landlord and Tenant, as tenant (the "***Gazelle Court Lease***") on which tenant under such Gazelle Court Lease can exercise the Purchase Options (as defined in the Gazelle Court Lease) pursuant to the terms of Section 24.2.1 of the Gazelle Court Lease (each a "***Faraday Purchase Option***"). The day on which each Faraday Purchase Option shall close shall be the date on which the equivalent Purchase Option under the Gazelle Court Lease is required to close. Each such date shall be referred to herein as the "***Faraday Purchase Option Closing Date***" for each applicable Faraday Purchase Option. Tenant's exercise of a Faraday Purchase Option shall be subject to and in accordance with the terms of this Section 24.3. For purposes of clarity, the exercise or expiration of a Faraday Purchase Option under the Lease will have no effect on Tenant's rights or obligations under the Gazelle Court Lease, and *vice versa*.

24.3.2 Tenant shall have no right to exercise any Faraday Purchase Option, or consummate any acquisition pursuant thereto, (a) during any period when a Tenant default exists and is continuing under the Lease, or (b) if the Lease has expired or otherwise been terminated. The rights contained in this Section 24.3 shall be personal to Tenant or to any assignee pursuant to a Specially Permitted Assignment, and shall automatically become null and void upon any transfer or assignment by the Tenant (other than a Specially Permitted Assignment).

24.3.3 If Tenant chooses to exercise any Faraday Purchase Option, then (a) the closing date for the purchase of the Premises shall be the respective Faraday Purchase Option Closing Date, and (b) Tenant shall deliver written notice to Landlord of Tenant's decision to exercise the Faraday Purchase Option (the "***Faraday Purchase Option Exercise Notice***") at least ninety (90) days prior to such Faraday Purchase Option Closing Date. If Tenant exercises any Faraday Purchase Option, but the closing of Tenant's purchase of the Premises does not occur by the Faraday Purchase Option Closing Date (for any reason other than due to the material default of Landlord hereunder or under the applicable Purchase and Sale Agreement or a failure of conditions for the benefit of Tenant), then the Faraday Purchase Option exercised by Tenant (and all other Faraday Purchase Options under this Lease) shall automatically lapse and be of no further force or effect, and Tenant shall have no further rights under this Section 24.3.

24.3.4 Upon Landlord's receipt of the Faraday Purchase Option Exercise Notice from Tenant, Landlord and Tenant shall execute a purchase and sale agreement for the Premises substantially in the form attached hereto as Exhibit 'A' (the "***Purchase and Sale Agreement***"). In connection with such purchase and sale, Tenant shall reimburse Landlord for all reasonable and customary costs actually incurred by Landlord in connection with the purchase and sale transaction including, but not limited to, attorneys' fees for outside counsel (provided, however, that Tenant will not be required to reimburse Landlord's attorneys' fees in excess of $25,000 (as such amount shall be adjusted by multiplying the amount by the CPI Adjustment Factor described below)). As used herein, the "***CPI Adjustment Factor***" means, as of any date, the greater of (a) the CPI for such date divided by the CPI for the Effective Date; and (b) 1.00. As used herein, "***CPI***" means the United States Department of Labor, Bureau of Labor Statistics "Consumer Price Index" for All Urban Consumers (CPI-U) published for the Los Angeles-

Riverside-Orange County, CA, Metropolitan Statistical Area, with a base of 1982-1984 = 100. If the CPI ceases to be published, with no successor index, then the parties shall reasonably agree upon a reasonable substitute index. The CPI for any date means the CPI last published before the calendar month that includes such date

24.3.5 The purchase price payable by Tenant for the acquisition of the Premises pursuant to the Faraday Purchase Option shall be as follows:

(a) With regard to any acquisition of the Premises pursuant to the Faraday Purchase Option at the end of Lease Year five (5), six (6), seven (7), eight (8) or nine (9) (as defined and set forth in the Gazelle Court Lease), the purchase price shall be calculated as of the applicable Faraday Purchase Option Closing Date by dividing the Base Monthly Rental due under the Lease for the twelve months following such Faraday Purchase Option Closing Date by the "cap rate" for the relevant Purchase Option under the Gazelle Court Lease set forth in the PO Model (as defined in the Gazelle Court Lease). Promptly following the Completion Date (as defined in the Gazelle Court Lease), the parties will discuss and endeavor to agree upon the applicable purchase price for the Faraday Purchase Options at the end of Lease Years five (5), six (6), seven (7), eight (8) and nine (9) (as defined and set forth in the Gazelle Court Lease), and the parties will by written amendment append such purchase prices to the Lease as a new Exhibit. If the parties are unable to agree upon the applicable purchase price, then the Lease shall continue in full force and effect until such purchase price is agreed upon. If the date on which such purchase price is agreed upon is after the applicable Faraday Purchase Option Closing Date has passed then the closing shall occur on the date that is thirty days after such purchase price is agreed upon.

(b) With regard to any acquisition of the Premises pursuant to the Faraday Purchase Option at the end of Lease Year fifteen (15) or twenty (20) (as defined and set forth in the Gazelle Court Lease), the purchase price shall equal the "***fair market value***" for the Premises determined as of the date that is sixty (60) days prior to the Faraday Purchase Option Closing Date. For purposes of this Section 24.3.5, the "***fair market value***" of the Premises shall be determined by the mutual agreement of Landlord and Tenant. However, if Landlord and Tenant are unable to agree upon such fair market value by the sixtieth (60th) day prior to the Faraday Purchase Option Closing Date, then "***fair market value***" shall be determined by a process whereby (i) each party shall select an independent and licensed appraiser (who must be a qualified MAI appraiser) for the Premises (with at least ten (10) years experience appraising properties of similar type, use and location as the Premises) within fifteen (15) days of the sixtieth (60th) day prior to the Purchase Option Closing Date, (ii) each such appraiser shall prepare an appraisal of the Premises within fifteen (15) business days after their selection, (iii) if the appraisals of both appraisers with respect to the Premises differ by an amount equal to or less than five percent (5%) of the higher of the two appraisals, then the average of such appraisals shall be deemed to be the fair market value for the Premises for purposes of this Section 24.3, and (iv) if the appraisals of both appraisers with respect to the Premises differ by an amount that exceeds five percent (5%) of the higher of the two appraisals, then the two (2) selected appraisers shall agree upon the selection of a third appraiser who must be a qualified MAI appraiser (also with at least ten (10) years experience appraising properties of similar type, use and location as the Premises that is unaffiliated with either party hereto and that has not been retained or engaged by either party within the five (5) years preceding such appointment) within fifteen (15)

days of the date the second determination is sent in, who shall prepare an appraisal of the Premises within fifteen (15) business days after his or her selection, and such appraisal shall constitute the binding determination of fair market value for purposes of this Section 24.3.5; provided, however, that such appraisal may not be greater than the higher of the other appraisals or less than the lower of the other appraisals. If the two appraisers are unable to agree upon the selection of a third appraiser, then either Landlord or Tenant shall be entitled to apply to the presiding judge of the Superior Court of the County of San Diego, California for the selection of a third appraiser who shall be selected from a list of names of experienced appraisers submitted by Landlord or from a list of names submitted by Tenant, as the case may be, unless both Landlord and Tenant submit lists of names, in which case the Court, in its sole discretion, shall select the third appraiser from the lists. The cost of all appraisals performed in accordance with this Section 24.3 shall be paid by Tenant. Such determination of "***fair market value***" determined in accordance with this Section 24.3.5 shall be binding upon the parties.

(c) In addition to the purchase price payable by Tenant pursuant to this Section 24.3.5, as a condition to closing, Tenant shall pay all Rent owing to Landlord as of the applicable Faraday Purchase Option Closing Date.

24.3.6 It is the intent of the parties that the "***fair market value***" of the Premises be determined by using the appraisal valuation standards then commonly used by professional appraisers in determining fair market value of biomedical use properties in the state in which the Premises is located. Any appraiser appointed pursuant to this Article 24 shall be instructed to determine independently the fair market value of the Premises in accordance with the definition of the term set forth in this Section 24.3.6.

24.3.7 Time is of the essence in the performance of the parties' respective obligations contained in this Section 24.3.

24.3.8 Landlord and Tenant agree to execute such additional documents, including, without limitation, escrow instructions, and take such further actions, as may be reasonable and necessary to carry out the provisions of this Section 24.3.8.

24.3.9 Upon the consummation of the Tenant's acquisition of the Premises pursuant to any Purchase Option, without limiting any of the parties' respective rights and remedies under the Lease, this Lease shall terminate, and shall be of no further force or effect, except for those rights, obligations, and liabilities which expressly survive such termination or which have accrued prior to such termination."

4. Options to Extend. Article 36 of the Lease is hereby replaced in its entirety with the following:

"ARTICLE 36

OPTION TO EXTEND

36.1 Options To Extend. Tenant shall have the option to extend the term of this Lease for four (4) successive renewal periods of five (5) years each, subject to the following provisions:

36.1.1 Tenant shall have no right to exercise an option: (i) during the period commencing with the giving of any notice of default and continuing until said default is cured, (ii) during the period of time any Rent is unpaid, or (iii) in the event that Landlord has given three or more notices of separate monetary or material non-monetary breaches, whether or not the breaches are cured, during the twelve (12) months immediately preceding the exercise of the applicable option.

36.1.2 The period of time within which an option may be exercised shall not be extended or enlarged by reason of Tenant's inability to exercise an option because of the occurrence of one or more of the matters described in Section 36.1.1.

36.1.3 An option shall terminate and be of no further force or effect, notwithstanding Tenant's due and timely exercise of the option, if, after such exercise and prior to the commencement of the extended term, (i) Tenant fails to pay Rent for a period of thirty (30) days after such Rent becomes due, or (ii) an Event of Default occurs.

36.1.4 Tenant shall exercise an option by delivery of written notice to Landlord not less than twelve (12) months prior to the expiration of the Lease Term (as the same may have theretofor been extended by the exercise of a previous option pursuant to this Section 36). If said notice is not delivered within said time period, such option and all remaining options granted pursuant to this Section 36 shall automatically terminate and be of no further force or effect.

36.2 Rent During Option Periods.

36.2.1 Rent. The Base Monthly Rental payable by Tenant during any option period shall be the greater of: (a) 95% of the "***fair market rent"*** for the Premises at the commencement date of such option period, and (b) the Base Monthly Rental payable for the year immediately preceding the commencement date of such option period; provided, however, that the Base Monthly Rental payable during such option period shall be subject to the escalation provisions of Section 3.3 with the first such escalation occurring either (i) at the end of the second year of the extended term if the Base Monthly Rental is determined in accordance with Section 36.2.1(a) or (ii) upon the first day of the first year of the extended term if the Base Monthly Rental is determined in accordance with Section 36.2.1(b).

36.2.2 Fair Market Rent. For purposes if this Section 36.2.2, the "***fair market rent***" for the Premises shall be determined as of the date that is sixty (60) days prior to the first day of the first year of the extended term. If Landlord and Tenant cannot agree on the fair market rent of the Premises for any extension period by the sixtieth (60^{th}) day prior to the first day of the first year of the extended term, then, Landlord and Tenant shall each select, within fifteen (15) days of such sixtieth (60^{th}) day prior to the first day of the first year of the extended term, an appraiser who must be a qualified MAI appraiser with at least five (5) years experience appraising properties of similar type, use and location as the Premises to determine said "***fair market rent***." If one party fails to so designate an appraiser within the time required, the determination of "***fair market rent***" of the one appraiser who has been designated by the other party within the time required shall be binding on both parties. The appraisers shall submit their determinations of fair market rental value to both parties within fifteen (15) business days after

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their selection. If the difference between the two determinations is ten percent (10%) or less of the higher appraisal, then the average between the determinations shall be the fair market rental value of the Premises. If said difference is greater than ten percent (10%), then the two appraisers shall within fifteen (15) days of the date the second determination is submitted to the parties designate a third appraiser who must also be a qualified MAI appraiser with at least five (5) years experience appraising properties of similar type, use and location as the Premises that is unaffiliated with either party hereto and that has not been retained or engaged by either party within the five (5) years preceding such appointment. If the two appraisers are unable to agree upon the selection of a third appraiser, then either Landlord or Tenant shall be entitled to apply to the presiding judge of the Superior Court of the County of San Diego, California for the selection of a third appraiser who shall be selected from a list of names of experienced appraisers submitted by Landlord or from a list of names submitted by Tenant, as the case may be, unless both Landlord and Tenant submit lists of names, in which case the Court, in its sole discretion, shall select the third appraiser from the lists. The sole responsibility of the third appraiser will be to determine which of the determinations made by the first two appraisers is most accurate. The third appraiser shall have no right to propose a middle ground or any modification of either of the determinations made by the first two appraisers. The third appraiser's choice shall be submitted to the parties within fifteen (15) business days after his or her selection. Such determination shall bind both of the parties and shall establish the fair market rental value of the Premises. Each party shall pay equal shares of the fees and expenses of the third appraiser. Fair market rent for the purposes of this Lease shall mean the then prevailing rent for buildings in the Carlsbad, California life science market, of comparable size, quality and location to the demised Premises, and leased on terms comparable to the terms contained in this Lease."

5. Memorandum of Lease. Concurrently herewith, the parties shall promptly execute, acknowledge, and deliver duplicate originals of a Memorandum of Lease in form attached hereto as Exhibit 'B' (the ***"Memorandum of Lease"***). Either party may record such Memorandum of Lease. Any taxes imposed upon such recording shall be paid by Tenant. If the parties amend the Lease, then the parties shall have the same rights and obligations regarding a memorandum of such amendment as they do for the Memorandum of Lease. Except as provided in this Section 5, Tenant shall not file or record any other documents with respect to the Premises.

6. Exhibits. The provisions of Exhibits "A" and "B" attached hereto are hereby incorporated into and made a part of the Lease as Exhibits "E" and "F" thereto, respectively.

7. Broker. Landlord and Tenant each represents to the other that it has had no dealings with any real estate broker or agent in connection with the negotiation and/or execution of this Lease other than CresaPartners ("***Broker***"), and that they know of no other real estate broker or agent that is or might be entitled to a commission in connection with this Lease. Landlord shall compensate Broker in relation to this Lease pursuant to a separate agreement between Landlord and Broker.

8. No Default. Tenant represents, warrants and covenants that, to the best of Tenant's knowledge, Landlord and Tenant are not in default of any of their respective obligations under the Lease and no event has occurred that, with the passage of time or the giving of notice (or both) would constitute a default by either Landlord or Tenant thereunder.

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9. Effect of Amendment. Except as modified by this Amendment, the Lease and all the covenants, agreements, terms, provisions and conditions thereof shall remain in full force and effect and are hereby ratified and affirmed. The covenants, agreements, terms, provisions and conditions contained in this Amendment shall bind and inure to the benefit of the parties hereto and their respective successors and, except as otherwise provided in the Lease, their respective assigns. In the event of any conflict between the terms contained in this Amendment and the Lease, the terms herein contained shall supersede and control the obligations and liabilities of the parties. From and after the date hereof, the term "Lease" as used in the Lease shall mean the Lease, as modified by this Amendment.

10. Miscellaneous. This Amendment becomes effective only upon execution and delivery hereof by Landlord and Tenant. The captions of the paragraphs and subparagraphs in this Amendment are inserted and included solely for convenience and shall not be considered or given any effect in construing the provisions hereof. All exhibits hereto are incorporated herein by reference.

11. Counterparts. This Amendment may be executed in one or more counterparts that, when taken together, shall constitute one original.

IN WITNESS WHEREOF, Landlord and Tenant have hereunto set their hands as of the date and year first above written, and acknowledge that they possess the requisite authority to enter into this transaction and to execute this Amendment.

LANDLORD:

BMR-2282 FARADAY AVENUE LLC,
a Delaware limited liability company

By: */s/ John Bonanno*
Name: John Bonanno
Title: VP, Development

TENANT:

BMR-2282 FARADAY AVENUE LLC,
a Delaware corporation

By: */s/ B. Lynne Parshall*
Name: B. Lynne Parshall
Title: COO and CFO

EXHIBIT A TO AMENDMENT

EXHIBIT E

FORM PURCHASE AND SALE AGREEMENT

[See Attached]

AGREEMENT OF SALE

THIS AGREEMENT OF SALE (this "***Agreement***") is made the day of , 20 (the "***Effective Date***"), by and between **BMR-2282 FARADAY AVENUE LLC,** a Delaware limited liability company ("***Seller***"), and **ISIS PHARMACEUTICALS, INC.,** a Delaware corporation ("***Buyer***"). Seller and Buyer are sometimes hereinafter referred to collectively as the "***parties***".

W I T N E S S E T H

1. **Sale of Premises.**

A. Purchase and Sale. Subject to all of the terms and conditions of this Agreement, Seller agrees to sell and convey to Buyer, and Buyer agrees to purchase from Seller, any and all of Seller's right, title and interest in and to the following:

(i) the land located at 2282 Faraday Avenue, Carlsbad, California, as more fully described in Exhibit "A" attached hereto and made a part hereof, together with all strips and gores and any land lying in the bed of any street, road or alley, open or proposed, adjoining such real property (collectively, the "***Land***");

(ii) all and singular the rights, benefits, privileges, easements, tenements, hereditaments, and appurtenances thereon or in anyway appertaining to the Land (collectively, the "***Appurtenant Rights***");

(iii) buildings, structures, fixtures, systems, improvements, topsoil, trees, shrubbery and landscaping situated on, in or under or used in connection with the land (collectively, the "***Improvements***");

(iv) all right, title and interest of Seller, if any, in and to all tangible personal property now or hereafter located on, or used exclusively in connection with, the operation, ownership, maintenance, occupancy or improvement of the Land (collectively, the ***"Tangible Personal Property"***; and

(v) all right, title and interest of Seller, if any, in and to all intangible personal property now or hereafter used exclusively in connection with the operation, ownership, maintenance, management, or occupancy of the Land or Improvements (to the extent assignable); the plans and specifications for the Improvements (to the extent assignable); warranties, indemnities, guaranties (express or implied), applications, permits, authorizations, approvals and licenses (to the extent applicable in any way to the above referenced Land, Improvements or the Tangible Personal Property and assignable); insurance proceeds received by (or owed to) Seller which relate to damage to the Land or Improvements caused by a casualty that has occurred prior to the Closing Date and for which restoration has not previously occurred, but only to the extent that such proceeds have not been applied by Seller prior to the Closing Date towards the cost of (a) pursuit or settlement of the applicable insurance claim, (b) the clearing of debris or other expenses associated with securing the Land or Improvements, or (c) restoration of the Land or Improvements; and condemnation awards or claims thereto (collectively, the "***Intangible Property***").

B. Premises Defined. The Land, the Appurtenant Rights, the Improvements, the Tangible Personal Property and the Intangible Property are hereinafter referred to as the "***Premises***".

2. **Purchase Price.** The purchase price for the Premises (the "***Purchase Price***") shall be Dollars ($), payable as follows:

A. Deposit. Concurrently with the execution and delivery of this Agreement, (i) the parties shall establish an escrow (the "***Escrow***") with [Chicago Title Insurance Company, 2365 Northside Drive, 6th Floor, San Diego, CA 92108, Attn: Renee Marshall] (the "***Title Company***"), (ii) the parties shall deposit with the Title Company a fully executed original of this Agreement, and (iii) Buyer shall deposit with the Title Company a sum equal to [Dollars ($)] **[INSERT AMOUNT THAT IS [***] OF THE PURCHASE PRICE]** in good funds either by certified bank or cashier's check or by federal wire transfer (such funds, together with all interest accrued thereon while held in Escrow, the "***Deposit***"). The Deposit shall be held in escrow by the Title Company in a federally insured, interest bearing account in accordance with the laws of the State of California and the provisions of this Agreement. If this Agreement is terminated pursuant to Section 7 hereof, the Deposit shall be paid to either Buyer or Seller in accordance with the provisions of Section 7. If the sale of the Premises is consummated, the Deposit shall be released to Seller and shall be credited against the Purchase Price.

B. Payment of Purchase Price. At Closing, the Deposit shall be released to Seller, and Buyer shall pay to Seller through Escrow in the manner described herein the balance of the Purchase Price, as adjusted for prorations and other adjustments provided herein.

3. **Condition of Title.**

A. Title Review. Buyer acknowledges that it has been provided with the right and opportunity to review and investigate any and all conditions and aspect of title to the Premises deemed necessary or desirable by Buyer for purposes of evaluating the transactions contemplated hereby.

B. Title Examination. Buyer hereby acknowledges that it approves all the encumbrances and exceptions to title embodied in the Permitted Exceptions (as defined below), and Buyer shall take title to the Premises subject to all such Permitted Exceptions (as defined below); provided, however, that Seller shall cause any liens granted by Seller and encumbering the Premises to secure the repayment of borrowed money to be removed from title or otherwise insured over by the Title Company. Without limiting the effect of the foregoing, the parties acknowledge and agree that the term "***Permitted Exceptions***" shall include the following:

(i) the title encumbrances described on Exhibit F attached hereto;

(ii) all covenants, conditions, restrictions, reservations, rights, rights of way, dedications, offers of dedication, encumbrances, liens and easements, in each case whether filed in the applicable public records or as would be apparent from an inspection or accurate survey of the Premises, except in each case to the extent that the same are granted or caused by Seller in a manner that would constitute a breach under the Lease;

(iii) the rights of tenants or other occupants under any leases, licenses, and occupancy agreements granted by any person or entity other than Seller, including all amendments or modifications thereto or supplements thereof, covering all or any portion of the Premises;

(iv) the lien of all ad valorem real estate taxes and assessments;

(v) all liens and encumbrances with respect to the Premises which were granted by, or which arise in connection with the acts or omissions of, Buyer or any of Buyer's agents, contractors, affiliates, invitees, or any other party that Buyer has permitted to use or occupy the Land or Improvements from and after the Effective Date of the Lease (as such term is defined in the Lease);

(vi) local, state and federal laws, ordinances or governmental regulations, including but not limited to building and zoning laws, ordinances and regulations, now or hereafter in effect relating to the Premises; and

(vii) those matters which would be disclosed by an accurate survey or inspection of the Premises.

C. Conveyance of Title. At Closing, Seller shall convey and transfer, or cause to be conveyed or transferred, to Buyer all of Seller's right, title and interest in and to the Premises, subject to the Permitted Exceptions.

D. Covenants of Seller. Seller, as Landlord, and Buyer, as tenant, are parties to that certain Lease Agreement, dated as of September 19, 2005, as amended by that certain First Amendment to Lease Agreement dated as of May 8, 2007 and that certain Second Amendment to Lease Agreement dated as of March 30, 2010 (as so amended, the "***Lease***"), pursuant to which Buyer leases the Premises and is responsible for, among other things, its repair, upkeep and maintenance. Accordingly, Seller has not undertaken to either manage or operate the Premises in any particular way prior to Closing, or deliver the Premises at Closing in any particular condition. During the period from and after the Effective Date until the date that Closing occurs, Seller (i) shall fully and timely perform its obligations under the Lease, and (ii) shall not, without Buyer's consent (which will not be unreasonably withheld, conditioned or delayed), grant any new liens or encumbrances against the Premises or take any action which would have a material adverse effect on (a) the use of the Premises in the manner in which it is being used as of the Effective Date, or (b) the value of the Premises.

4. **Closing.** The consummation of the purchase and sale of the Premises contemplated by this Agreement (the "***Closing***") shall take place on [, 20] (the "***Closing Date***") at [1:00 PM local time] through the Escrow administered by the Title Company, or such other time and place as Seller and Buyer agree to in writing. **[NOTE: TO BE DETERMINED IN ACCORDANCE WITH SECTION 24.3 OF THE LEASE].**

A. Conditions to Seller's Obligation to Close. The obligation of Seller to consummate the transactions contemplated hereunder shall be contingent upon the following:

(i) Representations. Buyer's representations and warranties contained herein shall be materially true and correct as of the date of this Agreement;

(ii) Performance. All deliveries to be made by Buyer at Closing have been tendered, and Buyer shall have performed all of the other obligations to be performed by Buyer under this Agreement; and

(iii) Moratorium. No moratorium, statute or regulation of any governmental agency or order or ruling of any court has been enacted, adopted, or issued which would adversely affect Buyer's ability to purchase the Property from Seller.

B. Conditions to Buyer's Obligation to Close. The obligation of Buyer to consummate the transactions contemplated hereunder shall be contingent upon the following:

(i) Representations. Seller's representations and warranties contained herein shall be materially true and correct as of the date of this Agreement;

(ii) Performance. All deliveries to be made by Seller at Closing have been tendered, and Seller shall have performed all of the other obligations to be performed by Seller under this Agreement;

(iii) Title. Upon the sole condition of payment of the premium, at Closing, the Title Company shall have irrevocably and unconditionally committed to issue to Buyer an ALTA Owner's Policy of title insurance, with extended coverage (i.e., with ALTA General Exceptions deleted), dated as of the date and time of the recording of the Deed (as defined below), in the amount of the Purchase Price, insuring Buyer as owner of good, marketable and indefeasible fee simple title to the Property, subject only to the Permitted Exceptions; provided, however, that notwithstanding the foregoing or any other provision of this Agreement to the contrary, the parties agree that Seller shall not be required to provide any indemnities, representations, warranties or affidavits to the Title Company; and

(iv) Moratorium. No moratorium, statute or regulation of any governmental agency or order or ruling of any court has been enacted, adopted, or issued which would adversely affect Seller's ability to sell the Property to Buyer.

C. Failure of Condition Precedent. If any condition to such party's obligation to proceed with the Closing hereunder has not been satisfied as of the Closing Date; each non-defaulting party may, in its sole discretion, either (i) terminate this Agreement by delivering written notice to the other party, or (ii) elect to close, notwithstanding the non-satisfaction of such condition, in which event such party shall be deemed to have waived any such condition.

5. **Provisions With Respect to Closing.**

A. Deliveries by Seller. At least one (1) business day prior to the Closing Date, Seller shall deliver, or cause to be delivered, to the Title Company, to be held in Escrow pending Closing, each of the following:

(i) Deed. One (1) original Grant Deed, duly executed and acknowledged by Seller, substantially in the form of Exhibit "B" attached hereto (the "***Deed***");

(ii) Bill of Sale and Assignment of Warranties. Two (2) original counterparts of a Bill of Sale and Assignment and Assumption of Warranties, duly executed by Seller, substantially in the form of Exhibit "C" attached hereto ("***Bill of Sale and Assignment of Warranties***");

(iii) Termination of Lease. Two (2) original counterparts of a Termination of Lease Agreement, duly executed by Seller substantially in the form of Exhibit "D" attached hereto ("***Lease Termination***");

(iv) FIRPTA Affidavit. One (1) original Certificate Regarding Foreign Investment in Real Property Tax Act, duly executed and acknowledged by Seller, substantially in the form of Exhibit "E" attached hereto.; and

(v) Closing Statement. An executed closing statement consistent with this Agreement and in a form requested by the Title Company.

B. Deliveries by Buyer. At least one (1) business day prior to the Closing Date, Buyer shall deliver, or cause to be delivered, to the Title Company, to be held in Escrow pending Closing, each of the following:

(i) Funds. The balance of the Purchase Price, as adjusted for prorations and other adjustments provided herein;

(ii) Bill of Sale and Assignment of Warranties. Two (2) original counterparts of the Bill of Sale and Assignment of Warranties, duly executed by Buyer;

(iii) Termination of Lease. Two (2) original counterparts of the Lease Termination, duly executed by Buyer;

(iv) Release. A release of claims, duly executed and acknowledged by Buyer that contains the same disclaimers and release as set forth in Section 11, except such release will be dated as of the Closing Date (the "***Release***"); and

(v) Closing Statement. An executed closing statement consistent with this Agreement and in a form requested by the Title Company.

6. **Closing Costs; Taxes; Apportionments.**

A. Buyer shall pay: (i) the fees of any counsel representing Buyer in connection with the transaction contemplated by this Agreement (the "***Transaction***"); (ii) the fees of any counsel representing Seller in connection with the Transaction (provided, however, that Buyer shall not be required to pay such fees in excess of $25,000 (as such amount shall be adjusted by multiplying $25,000 by the CPI Adjustment Factor described below)); (iii) the escrow fee, if any, which may be charged by the Title Company; (iv) the costs of any title reports, commitments or policies that Buyer may elect to obtain; (v) the cost of any survey that Buyer may elect to obtain; (v) all of the recording fees in connection with the sale transaction, and (vi) any transfer and sales taxes (but excluding Seller's federal or state income, franchise, inheritance or estate taxes) that may arise in connection with the Transaction. As used herein, the "***CPI Adjustment Factor***" means, as of Closing Date, the greater of (a) the CPI for such date divided by the CPI for the Effective Date of the Lease; and (b) 1.00. As used herein, "***CPI***" means the United States Department of Labor, Bureau of Labor Statistics "Consumer Price Index" for All Urban Consumers (CPI-U) published for the Los Angeles-Riverside-Orange County, CA, Metropolitan Statistical Area, with a base of 1982-1984 = 100. If the CPI ceases to be published, with no successor index, then the parties shall reasonably agree upon a reasonable substitute index. The CPI for any date means the CPI last published before the calendar month that includes such date.

B. Seller shall pay the fees of any counsel representing Seller to the extent that such fees exceed the amount of Seller's legal fees for which Buyer is responsible pursuant to Section 6(A)(ii) above.

C. Prorations. If the Purchase Price is received by Seller's depository bank in time to credit to Seller's account on the Closing Date, the day of Closing shall belong to Buyer and all prorations hereinafter provided to be made as of the Closing shall each be made as of the end of the day before the Closing Date. If the cash portion of the Purchase Price is not so received by Seller's depository bank on the Closing Date, then the day of Closing shall belong to Seller and such proration shall be made as of the end of the day that is the Closing Date. In each such proration set forth below, the portion thereof applicable to periods beginning as of Closing shall be credited to Buyer or charged to Buyer as applicable and the portion thereof applicable to periods ending as of Closing shall be credited to Seller or charged to Seller as applicable. The parties acknowledge and agree that the Lease is a fully triple net lease such that Buyer, as tenant, is responsible to pay directly, or reimburse Seller for, any and all expenses incident to the ownership, operation and maintenance of the Premises, in each case as required under the Lease. As a result, the parties shall not engage in normal and customary prorations. However, at Closing, Buyer shall pay or credit to Seller any and all of the following: (i) all Rent (as defined in the Lease) owing from Buyer, as tenant, to Seller (such amounts, "***Rental Amounts***") under

the Lease for the portion of the month in which closing occurs occurring prior to Closing and any period prior to Closing to the extent not previously paid by Buyer to Seller, including, but not limited to, any rental delinquencies; and (ii) all sums advanced or paid by Seller for real estate taxes, operating expenses, general assessments or special assessments related to the Premises for any period prior to or subsequent to the Closing to the extent not previously paid or reimbursed by Buyer, including, but not limited to, real estate taxes paid by Seller with respect to any period prior to or subsequent to the Closing and not yet reimbursed. At Closing, Seller shall credit to Buyer any Rental Amounts paid by Buyer that are allocable to the period from and after Closing; provided, however, that Seller shall retain all amounts of additional rent previously paid by Buyer to Seller on account of common area maintenance expenses, real estate taxes, insurance expenses or other expenses to the extent incurred by Seller on account of expenses allocable to the Premises prior to or after Closing and previously paid by Seller.

D. Final Adjustment After Closing. In the event that final bills are not available or cannot be issued prior to Closing for any item being prorated under this Article 6, then Buyer and Seller agree to allocate such items on a fair and equitable basis as estimated based on the previous year's amounts, with a true-up and final adjustment to be made as soon as reasonably possible after the Closing but no later than [six (6)] months after Closing. Payments in connection with the final adjustment shall be due within thirty (30) days after receipt of written notice. Each party shall have reasonable access to, and the right to inspect and audit, the other party's books to confirm the final prorations.

7. **Failure to Close; Defaults.**

A. Buyer's Default. Provided that Seller has materially complied with its obligations hereunder and the conditions set forth in Section 4B have been satisfied, if Buyer fails to complete the Closing in accordance with the terms of this Agreement, then in addition to (i) any rights or remedies that Seller may have in connection therewith under the Lease, and (ii) any loss of rights that Buyer may incur in connection therewith and under the

Lease (collectively, the "***Lease Implications***"), the Deposit shall be retained by Seller as liquidated and agreed damages for such breach, which shall be Seller's sole and exclusive right and remedy under this Agreement for such breach, whereupon this Agreement shall become null and void and neither party hereto shall have any further rights, liabilities or obligations hereunder except those obligations which expressly survive termination

THE PARTIES ACKNOWLEDGE THAT SELLER'S ACTUAL DAMAGES IN THE EVENT THE SALE IS NOT CONSUMMATED ARE EXTREMELY DIFFICULT OR IMPRACTICABLE TO DETERMINE AT THE EFFECTIVE DATE. THEREFORE, BY SEPARATELY EXECUTING THIS SECTION 7(A) BELOW, THE PARTIES ACKNOWLEDGE THAT THE AMOUNT OF THE DEPOSIT HAS BEEN AGREED UPON, AFTER NEGOTIATION, AS THE PARTIES' REASONABLE ESTIMATE OF SELLER'S DAMAGES AND NOT A PENALTY, AND SHALL (ASIDE FROM THE LEASE IMPLICATIONS, WHICH SHALL NOT BE LIMITED IN ANY WAY BY THIS SECTION BE SELLER'S SOLE AND EXCLUSIVE REMEDY AGAINST BUYER ARISING FROM A FAILURE OF THE SALE TO CLOSE. IN ADDITION, BUYER SHALL PAY ALL COSTS AND EXPENSES ALLOCABLE TO BUYER PURSUANT TO SECTION 6(A), AS WELL AS

ALL TITLE AND ESCROW CANCELLATION CHARGES. NOTWITHSTANDING THE FOREGOING, IN NO EVENT SHALL THIS SECTION 7(A) LIMIT THE DAMAGES RECOVERABLE BY EITHER PARTY AGAINST THE OTHER PARTY DUE TO THE OTHER PARTY'S OBLIGATION TO INDEMNIFY SUCH PARTY IN ACCORDANCE WITH SECTION 14 OF THIS AGREEMENT. BY SEPARATELY EXECUTING THIS SECTION 7(A). BELOW, BUYER AND SELLER ACKNOWLEDGE THAT THEY HAVE READ AND UNDERSTOOD THE ABOVE PROVISION COVERING LIQUIDATED DAMAGES, AND THAT EACH PARTY WAS REPRESENTED BY COUNSEL WHO EXPLAINED THE CONSEQUENCES OF THIS LIQUIDATED DAMAGES PROVISION AT THE TIME THIS AGREEMENT WAS EXECUTED.

BMR-2282 FARADAY AVENUE LLC	**ISIS PHARMACEUTICALS, INC.**
By: _____	By: _____
Name: _____	Name: _____
Title: _____	Title: _____

B. Seller's Default. In the event that Seller shall fail to perform the acts required by this Agreement to be performed by it prior to or as of the Closing for any reason, or the conditions set forth in Section 4B were not satisfied for any reason, Buyer shall be entitled, as its sole and exclusive remedy, to (i) receive the return of the Deposit, which return shall operate to terminate this Agreement and release Seller from any and all liability hereunder, or (ii) to enforce specific performance of Seller's obligation to convey the Premises to Buyer as contemplated by this Agreement, it being understood that the remedy of specific performance shall not be available to enforce any other obligation of Seller hereunder. Buyer shall be deemed to have elected to terminate this Agreement and receive the return of the Deposit as its sole and exclusive remedy if Buyer fails to file suit for specific performance against Seller in a court having jurisdiction in the county and state in which the Premises is located within sixty (60) days following the scheduled Closing Date.

8. **Seller's Representations, Warranties and Covenants.** Seller hereby represents, warrants and covenants to Buyer, as of the Effective Date, as follows:

A. Seller has full capacity, power and authority to execute and deliver this Agreement and to perform its obligations hereunder.

B. This Agreement, and all other instruments and documents to be executed and delivered by Seller to Buyer hereunder or pursuant hereto, have been or will be duly

executed and delivered by Seller and constitute (or will constitute, as to those instruments and documents to be executed and delivered) the legal, valid and binding obligations of Seller enforceable against Seller in accordance with their respective terms, subject to applicable bankruptcy, insolvency, fraudulent conveyance, reorganization, moratorium and similar laws affecting creditors' rights and remedies generally and general principals of equity.

C. There is no suit, action or proceeding pending or to the knowledge of Seller threatened against Seller before or by any court, administrative agency or other governmental or quasi-governmental authority, (i) affecting the Premises or (ii) which brings into question the validity of this Agreement or the Transaction.

9. **Buyer's Representations, Warranties and Covenants.** Buyer hereby represents, warrants and covenants to Seller, as of the Effective Date, as follows:

A. Buyer has full capacity, power and authority to execute and deliver this Agreement and to perform all of its obligations hereunder.

B. This Agreement and all other instruments and documents to be executed and delivered by Buyer to Seller hereunder or pursuant hereto have been or will be duly executed and delivered by Buyer and constitute (or will constitute, as to those instruments and documents to be executed and delivered) the legal, valid and binding obligations of Buyer enforceable against Buyer in accordance with their respective terms.

C. There is no suit, action or proceeding pending or to the knowledge of Buyer threatened against Buyer or affecting the Premises before or by any court, administrative agency or other governmental or quasi-governmental authority, or which brings into question the validity of this Agreement or the Transaction.

10. **Investigations.**

A. Buyer acknowledges that it (i) is familiar with the Premises, (ii) has been given an opportunity to inspect the Premises and (iii) has completed all of its inspections with respect to the condition of the Premises as of the Effective Date.

11. **Disclaimers and Warranties.**

A. AS IS SALE; DISCLAIMERS. WITH RESPECT TO CLAUSES (i) THROUGH (iv) BELOW, EXCEPT IN THE CASE OF A BREACH BY SELLER OF THE REPRESENTATIONS AND WARRANTIES CONTAINED IN SECTION 8, AND EXCEPT FOR SELLER'S BREACH OF ITS COVENANT SET FORTH IN SECTION 3D:

i. SELLER IS NOT MAKING, AND HAS NOT AT ANY TIME MADE, ANY WARRANTIES OR REPRESENTATIONS OF ANY KIND OR CHARACTER, EXPRESS OR IMPLIED, WITH RESPECT TO THE PREMISES, INCLUDING, BUT NOT LIMITED TO, ANY WARRANTIES OR REPRESENTATIONS AS TO HABITABILITY, MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE.

ii. UPON CLOSING SELLER SHALL SELL AND CONVEY TO BUYER, AND BUYER SHALL ACCEPT, THE PREMISES "AS IS, WHERE IS, WITH ALL FAULTS". BUYER HAS NOT RELIED AND WILL NOT RELY ON, AND SELLER IS NOT LIABLE FOR OR BOUND BY, ANY EXPRESS OR IMPLIED WARRANTIES, GUARANTIES, STATEMENTS, REPRESENTATIONS OR INFORMATION PERTAINING TO THE PREMISES OR RELATING THERETO MADE OR FURNISHED BY SELLER OR ANY REAL ESTATE BROKER OR AGENT REPRESENTING OR PURPORTING TO REPRESENT SELLER, TO WHOMEVER MADE OR GIVEN, DIRECTLY OR INDIRECTLY, ORALLY OR IN WRITING. ALL MATERIALS, DATA AND INFORMATION DELIVERED BY SELLER TO BUYER, OR OTHERWISE MADE AVAILABLE TO BUYER, IN CONNECTION WITH THE TRANSACTION CONTEMPLATED HEREBY ARE PROVIDED TO BUYER AS A CONVENIENCE ONLY AND ANY RELIANCE ON OR USE OF SUCH MATERIALS, DATA OR INFORMATION BY BUYER SHALL BE AT THE SOLE RISK OF BUYER. NEITHER SELLER, NOR ANY AFFILIATE OF SELLER, NOR THE PERSON OR ENTITY WHICH PREPARED ANY REPORT OR REPORTS MADE AVAILABLE BY SELLER TO BUYER SHALL HAVE ANY LIABILITY TO BUYER FOR ANY INACCURACY IN OR OMISSION FROM ANY SUCH REPORTS. BUYER ACKNOWLEDGES THAT THE PURCHASE PRICE REFLECTS AND TAKES INTO ACCOUNT THAT THE PREMISES IS BEING SOLD "AS IS."

iii. BUYER REPRESENTS AND COVENANTS TO SELLER THAT BUYER HAS CONDUCTED SUCH INVESTIGATIONS OF THE PREMISES, INCLUDING BUT NOT LIMITED TO, THE PHYSICAL AND ENVIRONMENTAL CONDITIONS THEREOF, AS BUYER DEEMS NECESSARY OR DESIRABLE TO SATISFY ITSELF AS TO THE CONDITION OF THE PREMISES AND THE EXISTENCE OR NONEXISTENCE OF, OR CURATIVE ACTION TO BE TAKEN WITH RESPECT TO, ANY HAZARDOUS OR TOXIC SUBSTANCES ON OR DISCHARGED FROM THE PREMISES, AND WILL RELY SOLELY UPON SAME AND NOT UPON ANY INFORMATION PROVIDED BY OR ON BEHALF OF SELLER OR ITS AGENTS OR EMPLOYEES WITH RESPECT THERETO.

iv. UPON CLOSING, BUYER SHALL AUTOMATICALLY ASSUME THE RISK THAT ADVERSE MATTERS, INCLUDING BUT NOT LIMITED TO, CONSTRUCTION DEFECTS AND ADVERSE PHYSICAL AND ENVIRONMENTAL CONDITIONS, MAY NOT HAVE BEEN REVEALED BY BUYER'S INVESTIGATIONS, AND BUYER, UPON CLOSING, SHALL BE DEEMED TO HAVE WAIVED, RELINQUISHED AND RELEASED SELLER (AND SELLER'S AFFILIATES, PREDECESSORS, SUCCESSORS, PARTNERS, MEMBERS, OFFICERS, DIRECTORS, SHAREHOLDERS, TRUSTEES, EMPLOYEES, AGENTS, REPRESENTATIVES, LENDERS, CONSULTANTS AND ATTORNEYS) FROM AND AGAINST ANY AND ALL CLAIMS, DEMANDS, CAUSES OF ACTION IN LAW OR IN EQUITY (INCLUDING CAUSES OF ACTION IN TORT), LOSSES, DAMAGES, LIABILITIES, COSTS AND EXPENSES (INCLUDING REASONABLE ATTORNEYS' FEES) OF ANY AND EVERY KIND OR CHARACTER, KNOWN OR UNKNOWN, FIXED OR CONTINGENT, WHICH BUYER MIGHT HAVE ASSERTED OR ALLEGED AGAINST SELLER (AND SELLER'S AFFILIATES, PREDECESSORS, SUCCESSORS, PARTNERS, MEMBERS, OFFICERS,

DIRECTORS, SHAREHOLDERS, TRUSTEES, EMPLOYEES, AGENTS, REPRESENTATIVES, LENDERS, CONSULTANTS AND ATTORNEYS) AT ANY TIME BY REASON OF OR ARISING OUT OF ANY LATENT OR PATENT CONSTRUCTION DEFECTS OR PHYSICAL CONDITIONS, VIOLATIONS OF ANY APPLICABLE LAWS AND ANY AND ALL OTHER ACTS, OMISSIONS, EVENTS, CIRCUMSTANCES OR MATTERS REGARDING THE PREMISES. THE UNDERSIGNED ACKNOWLEDGES THAT IT HAS BEEN ADVISED BY LEGAL COUNSEL AND IS FAMILIAR WITH THE PROVISIONS OF CALIFORNIA CIVIL CODE SECTION 1542, WHICH PROVIDES AS FOLLOWS:

> "A GENERAL RELEASE DOES NOT EXTEND TO CLAIMS WHICH THE CREDITOR DOES NOT KNOW OR SUSPECT TO EXIST IN HIS OR HER FAVOR AT THE TIME OF EXECUTING THE RELEASE, WHICH IF KNOWN BY HIM OR HER MUST HAVE MATERIALLY AFFECTED HIS OR HER SETTLEMENT WITH THE DEBTOR."

THE UNDERSIGNED, BEING AWARE OF THIS CODE SECTION, HEREBY EXPRESSLY WAIVES ANY RIGHTS IT MAY HAVE THEREUNDER, AS WELL AS UNDER ANY OTHER STATUTES OR COMMON LAW PRINCIPALS OF SIMILAR EFFECT.

_____

Buyer's Initials

B. Survival of Disclaimers. The provisions of this Section 11 shall survive Closing or any termination of this Agreement.

12. **Notices.** All notices or other communications to be given by one party to the other under this Agreement shall be in writing, mailed or delivered to the other party at the following addresses:

If intended for Seller:

BMR-2282 FARADAY AVENUE LLC

Attn: Vice President, Real Estate Counsel
17190 Bernardo Center Drive
San Diego, California 92128
Phone: (858) 485-9840 Fax: (858) 485-9843

If intended for Buyer:

Isis Pharmaceuticals, Inc.
Attn: Chief Operating Officer
1896 Rutherford Road
Carlsbad, California 92008
Phone: (760) 931-9200 Fax: (760) 918-3599

with a copy to: General Counsel
Fax: 760-268-4922

Notices may be delivered by Federal Express, United Parcel Service, or other nationally recognized overnight (one-night) mail courier service, or sent by facsimile (provided a copy of such notice is deposited with an overnight courier for next business day delivery). Any such notice shall be considered given on the date of such hand or couriered delivery, confirmed facsimile transmission if received on a business day, deposit with such overnight courier for next business day delivery.

Either party may, with proper notice, at any time designate a different address to which notices shall be sent.

13. **Assignment.** Buyer may not assign its rights under this Agreement without first obtaining Seller's written approval, which approval may be given or withheld in Seller's sole discretion, *except* that Buyer may assign this agreement without Seller's approval but with written notice, to any (i) successor by merger or sale of substantially all of Buyer's assets (including, without limitation, this Agreement) in a manner such that the assignee will become liable and responsible for the performance and observance of all Buyer's duties and obligations hereunder; or (ii) corporation or other entity which controls, is controlled by, or is under common control with Buyer. In no event shall any assignment of this Agreement release or discharge Buyer from any liability or obligation hereunder unless expressly agreed otherwise by Seller in writing. Any transfer, directly or indirectly, (whether by merger, consolidation or otherwise) of any stock, partnership interest or other ownership interest in Buyer or any other transaction, in each case which results (whether directly or indirectly) in a change in control of Buyer shall constitute an assignment of this Agreement.

14. **Brokerage.** Each of Seller and Buyer represents and warrants to the other of them that it has not dealt with any broker, agent, finder or other intermediary in connection with the conveyance of the Premises or this Agreement. Each of Seller and Buyer agrees to indemnify, defend and hold the other harmless of, from and against any damages, costs, claims, losses or liabilities whatsoever (including attorney's fees, expenses and court costs) arising from any breach by the indemnifying party of the foregoing warranties, representations and agreements. This Section shall survive Closing under this Agreement.

15. **Time of the Essence.** Time, wherever mentioned herein, shall be of the essence of this Agreement.

16. **Binding Effect.** This Agreement shall be binding upon and inure to the benefit of Seller and Buyer and their respective successors, heirs and assigns.

17. **Entire Agreement.** This Agreement constitutes the entire agreement between the parties hereto regarding the transaction contemplated hereby and there are no other terms, covenants, conditions, warranties, representations or statements, oral or otherwise, of any kind whatsoever. Any agreement hereafter made shall be ineffective to change, modify, discharge or effect an abandonment of this Agreement in whole or in part unless such agreement is in writing and signed by the party against whom enforcement of the change, modification, discharge or abandonment is sought.

18. **Headings.** The headings incorporated in this Agreement are for convenience and reference only and are not a part of this Agreement and do not in any way control, define, limit, or add to the terms and conditions hereof.

19. **Governing Law.** This Agreement shall be construed, interpreted and governed by the laws of the State of California.

20. **Counterparts.** This Agreement may be executed in any number of counterparts, each of which shall be an original, and such counterparts together shall constitute one and the same instrument.

21. **Attorneys' Fees.** If either party commences an action against the other party arising out of or in connection with this Agreement, then the prevailing party shall be entitled to have and recover from the other party reasonable attorneys' fees, charges and disbursements and costs of suit in proportion to [***] up to a maximum of 100%; provided, however, that in the case where the prevailing party is awarded any equitable relief, then the prevailing party

may recover the full amount of such costs and attorney's fees. For example, if the prevailing party [***] and no equitable relief, but [***], and the prevailing party had two hundred thousand dollars ($200,000) in costs and attorneys' fees, then such prevailing party would be entitled to recover [***] of such costs and attorneys' fees.

[REMAINDER OF PAGE INTENTIONALLY LEFT BLANK]

IN WITNESS WHEREOF, the parties hereto have duly executed this Agreement, under seal, as of the day and year first-above written.

SELLER:
BMR-2282 FARADAY AVENUE LLC,
a Delaware limited liability company,

By: _____
Name: _____
Title: _____

BUYER:
ISIS PHARMACEUTICALS, INC.,
a Delaware corporation,

By: _____
Name: _____
Title: _____

ACKNOWLEDGMENT AND CONSENT OF TITLE COMPANY

On this day of , 20 , the undersigned, the Title Company named in the foregoing Agreement, intending to be legally bound hereby, agrees to keep, observe and perform the terms and conditions of said Agreement relating to the holding and disbursement of the Deposit (as defined in the Agreement), together with any interest earned thereon, and all additional monies paid to it in escrow pursuant to the terms and conditions thereof. Title Company shall not incur any liability to anyone for damages, losses, or expenses except for fraud, negligence or willful conversation in respect to any action taken or omitted in good faith. Title Company may tender into the registry of any court of competent jurisdiction any escrow funds if it deems that there is a dispute with respect to the disbursement of such funds. Thereafter, Title Company will be discharged from all further duties and liabilities hereunder.

TITLE COMPANY:

[ ]

By: _____

EXHIBIT "A"
(Legal Description of Premises)

Real property in the City of Carlsbad, County of San Diego, State of California, described as follows:

Parcel A:

Lot 7 of Carlsbad Tract No. 84-9, according to Map thereof No. 11230, filed in the Office of the County Recorder of San Diego County, May 10, 1985, as instrument no. 85-165947 of Official Records, and a portion of Parcel D of Parcel Map No. 14461, filed in the Office of the County Recorder of San Diego County, September 12, 1986 as instrument no. 86-402406 of Official Records; all in the City of Carlsbad, County of San Diego, State of California, more particularly described as follows:

Commencing at the Northwest corner of said Parcel D of Parcel Map No. 14461; thence along the Westerly property line of said Parcel D, South 18 degrees 26'06" East, 278.43 feet, to the true point of beginning; thence leaving said Westerly line North 50 degrees 30'00" East, 145.33 feet; thence North 70 degrees 12'00" East, 92.23 feet; thence South 39 degrees 30'48" East, 256.97 feet; thence South 50 degrees 29'12" West, 83.13 feet; thence South 71 degrees 33'54" West, 242.68 feet to a point on said Westerly property line; thence North 18 degrees 26'06" West, 215.24 feet to the true point of beginning.

Said property being described as “Parcel C” in a Certificate of Compliance recorded on April 21, 2003 as instrument no. 2003-0459192 of Official Records of said San Diego County.

Parcel B:

A non-exclusive easement on, over and under the common areas as defined and shown on those certain amended and restated declaration of establishment of Covenants, Conditions and Restrictions, and Reservation of Easements (the “Declarations”), dated June 28, 1988 and recorded August 8, 1988 as instrument no. 88-387705 of Official Records, for the purposes of ingress and egress, parking, the construction, installation, maintenance, removal replacements, operation and use of utilities, including but not limited to sewers, water and gas pipes, drainage lines and systems, electric power, conduit lines and wiring, telephone, conduits, lines and wires and other utilities, public or private, beneath the ground surface (except vaults, vents, access, structures and other facilities required to be above ground), subject to the terms, as more particularly set forth in the Declaration.

APN: 212-061-33-00

EXHIBIT “B”

FORM OF DEED

RECORDING REQUESTED BY
AND WHEN RECORDED MAIL TO:

The undersigned Grantor declares: documentary transfer tax not shown pursuant to Section 11932 of the Revenue and Taxation Code, as amended

GRANT DEED

FOR VALUE RECEIVED, BMR-2282 FARADAY AVENUE LLC, a Delaware limited partnership (“**Grantor**”), grants to ISIS PHARMACEUTICALS, INC., a Delaware corporation (“Grantee”), all that certain real property (the “**Property**”) situated in the City of Carlsbad, County of San Diego, State of California, described on Exhibit A attached hereto and by this reference incorporated herein, subject to all covenants, conditions, easements, encumbrances and all other matters affecting the Property.

IN WITNESS WHEREOF, the undersigned has executed this Grant Deed dated as of , 20 .

BMR-2282 FARADAY AVENUE LLC,
a Delaware limited liability company

By: _____
Name: _____
Title: _____

STATE OF CALIFORNIA }
COUNTY OF } *S.S.*

On , before me,
&nbs p;
, a Notary Public in and for said County and State, personally appeared,
;
&nb sp;
, who proved to me on the basis of satisfactory evidence to be the person(s) whose name(s) is/are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity(ies), and that by his/her/their signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

I certify under PENALTY OF PERJURY under the laws of the State of California that the foregoing paragraph is true and correct.

WITNESS my hand and official seal.

Signature: _____

(Notary Seal)

EXHIBIT A TO FORM OF DEED

DESCRIPTION OF PROPERTY

Real property in the City of Carlsbad, County of San Diego, State of California, described as follows:

Parcel A:

Lot 7 of Carlsbad Tract No. 84-9, according to Map thereof No. 11230, filed in the Office of the County Recorder of San Diego County, May 10, 1985, as instrument no. 85-165947 of Official Records, and a portion of Parcel D of Parcel Map No. 14461, filed in the Office of the County Recorder of San Diego County, September 12, 1986 as instrument no. 86-402406 of Official Records; all in the City of Carlsbad, County of San Diego, State of California, more particularly described as follows:

Commencing at the Northwest corner of said Parcel D of Parcel Map No. 14461; thence along the Westerly property line of said Parcel D, South 18 degrees 26'06" East, 278.43 feet, to the true point of beginning; thence leaving said Westerly line North 50 degrees 30'00" East, 145.33 feet; thence North 70 degrees 12'00" East, 92.23 feet; thence South 39 degrees 30'48" East, 256.97 feet; thence South 50 degrees 29'12" West, 83.13 feet; thence South 71 degrees 33'54" West, 242.68 feet to a point on said Westerly property line; thence North 18 degrees 26'06" West, 215.24 feet to the true point of beginning.

Said property being described as "Parcel C" in a Certificate of Compliance recorded on April 21, 2003 as instrument no. 2003-0459192 of Official Records of said San Diego County.

Parcel B:

A non-exclusive easement on, over and under the common areas as defined and shown on those certain amended and restated declaration of establishment of Covenants, Conditions and Restrictions, and Reservation of Easements (the "Declarations"), dated June 28, 1988 and recorded August 8, 1988 as instrument no. 88-387705 of Official Records, for the purposes of ingress and egress, parking, the construction, installation, maintenance, removal replacements, operation and use of utilities, including but not limited to sewers, water and gas pipes, drainage lines and systems, electric power, conduit lines and wiring, telephone, conduits, lines and wires and other utilities, public or private, beneath the ground surface (except vaults, vents, access, structures and other facilities required to be above ground), subject to the terms, as more particularly set forth in the Declaration.

APN: 212-061-33-00

EXHIBIT "C"
(Bill of Sale and Assignment and Assumption of Warranties)

THIS BILL OF SALE AND ASSIGNMENT AND ASSUMPTION OF WARRANTIES (the "Assignment") made as of this [ ] day of , 20 between BMR-2282 FARADAY AVENUE LLC, a Delaware limited liability company (the "Assignor"), and ISIS PHARMACEUTICALS, INC., a Delaware corporation ("Assignee"). Assignor and Assignee are parties to the Agreement of Purchase and Sale dated , between Assignor and Assignee (the "Agreement"). Capitalized terms used herein but not otherwise defined shall have the meanings ascribed thereto in the Agreement.

1. Assignor is the owner of that certain real property located in Carlsbad, California, more particularly described in Exhibit A attached hereto (the "Real Property"). Assignor hereby assigns, transfers, sets over and conveys to Assignee all of Assignor's right, title and interest, in, to, and under the following, in each case to the extent assignable without payment or fee: all warranties, indemnities, guaranties (express or implied), applications, permits, authorizations, approvals and licenses (to the extent applicable in any way to the above referenced Real Property and any improvements thereon (collectively, the **"**Warranties**"**).

2. Assignee does hereby assume and agree to perform all of Assignor's obligations under the Warranties accruing from and after the date hereof. Assignee agrees to indemnify, protect, defend and hold Assignor harmless from and against any and all liabilities, losses, costs, damages and expenses (including reasonable attorneys' fees) directly or indirectly arising out of or related to any breach or default in Assignee's obligations hereunder.

3. Sale of Personalty. For good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, Assignor hereby sells, transfers, sets over and conveys to Assignee the following:

(a) Tangible Personal Property. All right, title and interest of Assignor in and to all all tangible personal property now or hereafter located on, or used exclusively in connection with, the operation, ownership, maintenance, occupancy or improvement of the Land (collectively, the **"**Tangible Personal Property**"**; and

(b) Intangible Property. The following property to the extent assignable: All, right, title and interest of Assignor, if any, in and to all intangible personal property now or hereafter used exclusively in connection with the operation, ownership, maintenance, management, or occupancy of the Real Property (to the extent assignable); the plans and specifications for the Improvements (to the extent assignable); insurance proceeds received by (or owed to) Seller which relate to damage to the Land or Improvements caused by a casualty that has occurred prior to the Closing Date and for which restoration has not previously occurred, but only to the extent that such proceeds have not been applied by Seller prior to the Closing Date towards the cost of (a) pursuit or settlement of the applicable insurance claim, (b) the clearing of debris or other expenses associated with securing the Land or Improvements, or (c) restoration of the Land or Improvements; and condemnation awards or claims thereto.

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4. This Assignment shall be binding upon and inure to the benefit of Assignor and Assignee and their respective heirs, executors, administrators, successors and assigns.

5. This Assignment may be executed in two or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument.

[REMAINDER OF PAGE INTENTIONALLY LEFT BLANK]

IN WITNESS WHEREOF, Assignor and Assignee have each executed this Assignment as of the date first written above.

ASSIGNOR:

BMR-2282 FARADAY AVENUE LLC,
a Delaware limited liability company

By: _____
Name: _____
Title: _____

ASSIGNEE:

ISIS PHARMACEUTICALS, INC.,
a Delaware corporation

By: _____
Name: _____
Title: _____

EXHIBIT A TO FORM OF ASSIGNMENT AND ASSUMPTION OF WARRANTIES

DESCRIPTION OF PREMISES

Real property in the City of Carlsbad, County of San Diego, State of California, described as follows:

Parcel A:

Lot 7 of Carlsbad Tract No. 84-9, according to Map thereof No. 11230, filed in the Office of the County Recorder of San Diego County, May 10, 1985, as instrument no. 85-165947 of Official Records, and a portion of Parcel D of Parcel Map No. 14461, filed in the Office of the County Recorder of San Diego County, September 12, 1986 as instrument no. 86-402406 of Official Records; all in the City of Carlsbad, County of San Diego, State of California, more particularly described as follows:

Commencing at the Northwest corner of said Parcel D of Parcel Map No. 14461; thence along the Westerly property line of said Parcel D, South 18 degrees 26'06" East, 278.43 feet, to the true point of beginning; thence leaving said Westerly line North 50 degrees 30'00" East, 145.33 feet; thence North 70 degrees 12'00" East, 92.23 feet; thence South 39 degrees 30'48" East, 256.97 feet; thence South 50 degrees 29'12" West, 83.13 feet; thence South 71 degrees 33'54" West, 242.68 feet to a point on said Westerly property line; thence North 18 degrees 26'06" West, 215.24 feet to the true point of beginning.

Said property being described as "Parcel C" in a Certificate of Compliance recorded on April 21, 2003 as instrument no. 2003-0459192 of Official Records of said San Diego County.

Parcel B:

A non-exclusive easement on, over and under the common areas as defined and shown on those certain amended and restated declaration of establishment of Covenants, Conditions and Restrictions, and Reservation of Easements (the "Declarations"), dated June 28, 1988 and recorded August 8, 1988 as instrument no. 88-387705 of Official Records, for the purposes of ingress and egress, parking, the construction, installation, maintenance, removal replacements, operation and use of utilities, including but not limited to sewers, water and gas pipes, drainage lines and systems, electric power, conduit lines and wiring, telephone, conduits, lines and wires and other utilities, public or private, beneath the ground surface (except vaults, vents, access, structures and other facilities required to be above ground), subject to the terms, as more particularly set forth in the Declaration.

APN: 212-061-33-00

EXHIBIT "D"

LEASE TERMINATION AGREEMENT

THIS TERMINATION AGREEMENT (this "Agreement") is entered into as of , 20[ ], by and between BMR-2282 FARADAY AVENUE LLC, a Delaware limited liability company ("Landlord"), and ISIS PHARMACEUTICALS, INC., a Delaware corporation ("Tenant" and, together with Landlord, the "Parties").

RECITALS:

A. The Parties entered into that certain Lease Agreement, dated as of September 19, 2005, as amended by that certain First Amendment to Lease Agreement dated as of May 8, 2007 and that certain Second Amendment to Lease Agreement dated as of March 30, 2010 (as amended, the "Lease"). All capitalized terms used and not otherwise defined herein shall have the meanings ascribed thereto in the Lease.

B. The Parties now wish to terminate the Lease on the terms and conditions set forth herein.

NOW, THEREFORE, the Parties to this Agreement hereby agree as follows:

1. TERMINATION OF THE LEASE. EFFECTIVE AS OF , 20 (THE "EFFECTIVE DATE"), THE LEASE IS TERMINATED BY CONSENT OF THE PARTIES; PROVIDED, HOWEVER, THAT SUCH TERMINATION SHALL NOT TERMINATE OR LIMIT THE EFFECT OF THOSE PROVISIONS OF THE LEASE WHICH BY THEIR TERMS SURVIVE EXPIRATION OR TERMINATION OF THE LEASE.

2. ENTIRE AGREEMENT. THIS AGREEMENT SHALL CONSTITUTE THE FINAL, COMPLETE AND EXCLUSIVE EXPRESSION OF THE INTENTIONS OF THE PARTIES HERETO WITH RESPECT TO THE SUBJECT MATTER HEREOF AND SHALL SUPERSEDE ALL PREVIOUS COMMUNICATIONS, REPRESENTATIONS, AGREEMENTS, PROMISES OR STATEMENTS, EITHER ORAL OR WRITTEN, BY OR BETWEEN ANY PARTY WITH REGARD TO THE SUBJECT MATTER HEREOF.

3. COUNTERPARTS. THIS AGREEMENT MAY BE EXECUTED IN ONE OR MORE COUNTERPARTS, EACH OF WHICH SHALL BE READ TOGETHER AND BE CONSTRUED AS ONE INSTRUMENT. A FACSIMILE OR OTHER ELECTRONIC COPY OF A SIGNATURE SHALL BE AS BINDING AS AN ORIGINAL SIGNATURE.

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IN WITNESS WHEREOF, the parties have executed and delivered this Agreement as of the Effective Date.

LANDLORD:

BMR-2282 FARADAY AVENUE LLC,
a Delaware limited liability company

By: _____
Name: _____
Title: _____

TENANT:

ISIS PHARMACEUTICALS, INC.,
a Delaware corporation

By: _____
Name: _____
Title: _____

EXHIBIT "E"
(FIRPTA Affidavit)

CERTIFICATE REGARDING FOREIGN INVESTMENT IN REAL PROPERTY TAX ACT (ENTITY TRANSFEROR)

Section 1445 of the Internal Revenue Code provides that a transferee (purchaser) of a U.S. real property interest must withhold tax if the transferor (seller) is a foreign person. To inform the transferee (purchaser) that withholding tax is not required upon the disposition of a U.S. real property interest by BMR-2282 FARADAY AVENUE LLC, a Delaware limited liability company ("Transferor"). Transferor hereby certifies:

1. Transferor is not a foreign corporation, foreign partnership, foreign trust, or foreign estate (as those terms are defined in the Internal Revenue Code and Income Tax Regulations).

2. Transferor's Federal Employer Identification Number is .

3. Transferor's office address is:

17190 Bernardo Center Drive
San Diego, CA 92128

4. The address or description of the property which is the subject matter of the disposition is , Carlsbad, California.

Transferor understands that this certification must be disclosed to the Internal Revenue Service by transferee and that any false statement contained herein could be punished by fine, imprisonment, or both.

Transferor declares that it has examined this certification and to the best of its knowledge and belief, it is true, correct and complete, and further declares that the individual executing this certification on behalf of Transferor has full authority to do so.

BMR-2282 FARADAY AVENUE LLC,
a Delaware limited liability company

By: _____
Name: _____
Title: _____

EXHIBIT "F"
(Permitted Exceptions)

1. General and special taxes and assessments for the fiscal year 2005-2006, a lien not yet due or payable.

2. The lien of supplemental taxes, if any, assessed pursuant to Chapter 3.5 commencing with Section 75 of the California Revenue and Taxation Code, arising on or after the date of said policy.

3. Covenants, conditions, restrictions and easements in the document entitled "Third Amended and Restated Declaration of Covenants, Conditions and Restrictions of Carlsbad Research Center" recorded June 29, 1988 as Instrument No. 88-313420 of Official Records, which provide that a violation thereof shall not defeat or render invalid the lien of any first mortgage or deed of trust made in good faith and for value, but deleting any covenant, condition or restriction indicating a preference, limitation or discrimination based on race, color, religion, sex, handicap, familial status, national origin, sexual orientation, marital status, ancestry, source of income or disability, to the extent such covenants, conditions or restrictions violate Title 42, Section 3604(c), of the United States Codes or Section 12955 of the California Government Code. Lawful restrictions under state and federal law on the age of occupants in senior housing or housing for older persons shall not be construed as restrictions based on familial status.

4. The terms and provisions contained in the document entitled "Agreement Between Developer- Owner and the City of Carlsbad for the Payment of a Public Facilities Fee" recorded April 17, 1984 as Instrument No 84-140520 of Official Records.

5. An easement for public utilities and incidental purposes, recorded October 8, 1984 as Instrument No. 84-381176 of Official Records.
In Favor of: San Diego Gas and Electric Company, a corporation
Affects: A portion of said land

The location of the easement cannot be determined from record information.

6. An easement shown or dedicated on the map filed or recorded May 10, 1985 as Map No.11230 and map recorded September 12, 1986 as Parcel Map no. 14461
For: General utility and access and incidental purposes.

A portion of said easement has been vacated by Quitclaim Deed recorded October 27, 1986 as Instrument No. 86-485767 of Official Records.
Affects: Lot 8 of Map No. 11230

7. An easement shown or dedicated on the map filed or recorded May 10, 1985 as Map No. 11230 of Tract Maps

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For: Proposed General Access and Utility Easement and incidental purposes.

The location of the easement cannot be determined from record information.

8. The terms and provisions contained in the document entitled "Agreement Between Developer- Owner and the City of Carlsbad for the Payment of a Public Facilities Fee" recorded February 25, 1986 as Instrument No. 86-073170 of Official Records.

9. An easement for public utilities and incidental purposes, recorded March 4, 1986 as Instrument No. 86-084966 of Official Records.
In Favor of: San Diego Gas and Electric Company.
Affects: A portion of said land

The location of the easement cannot be determined from record information.

10. The right to relocate, from time to time, any such easement located on the common area, so long as any improvements constructed on such relocated easements are replaced, in favor of Carlsbad, Research Center, a California general partnership, as disclosed by document entitled "Grant Deed" Recorded January 19, 1988 as Instrument No. 88-024163 of Official Records.

11. Covenants, conditions, restrictions and easements in the document entitled "First Amended and Restated Declaration of Establishment of Covenants, Conditions and Restrictions and Reservation of Easements" recorded August 8, 1988 as Instrument No. 88-387705 of Official Records, which provide that a violation thereof shall not defeat or render invalid the lien of any first mortgage or deed of trust made in good faith and for value, but deleting any covenant, condition or restriction indicating a preference, limitation or discrimination based on race, color, religion, sex, handicap, familial status, national origin, sexual orientation, marital status, ancestry, source of income or disability, to the extent such covenants, conditions or restrictions violate Title 42, Section 3604(c), of the United States Codes or Section 12955 of the California Government Code. Lawful restrictions under state and federal law on the age of occupants in senior housing or housing for older persons shall not be construed as restrictions based on familial status.

    Document(s) declaring modifications thereof entitled "First Amendment to First Amended and Restated Declaration of Establishment of Covenants, Conditions and Restrictions and Reservation of Easements" recorded April 15, 1993 as Instrument No. 1993-0232850 of Official Records.

12. An easement for construct, reconstruct, operate, maintain and repair facilities designed for the general purpose of collecting, storing, transporting, pumping and treating all water, including surface water, stream water, flood water and ground water flowing into said facilities, and all natural and artificial drainage ditches and structures of any kind, whether above or below the surface of the ground and

incidental purposes, recorded August 8, 1994 as Instrument No. 1994¬0482604 of Official Records.
In Favor of: Carlsbad Municipal water District, a public agency.
Affects: A portion of said land

At the date of recording of the document, the parties thereto had no record interest in the land.

13. An easement for construct, reconstruct, operate, maintain and repair facilities designed for the general purpose of collecting, storing, transporting, pumping and treating all water, including surface water, stream water, flood water and ground water flowing into said facilities, and all natural and artificial drainage ditches and structures of any kind, whether above or below the surface of the ground and incidental purposes, recorded August 8, 1994 as Instrument No. 199+· 0482622 of Official Records.
In Favor of: Carlsbad Municipal water District, a public agency.
Affects: A portion of said land

At the date of recording of the document, the parties thereto had no record interest in the land.

14. The terms and provisions contained in the document entitled "Commercial Cable Television Access Agreement and Easement" recorded September 27, 1995 as Instrument No. 1995¬0432157 of Official Records.

15. An easement for public utilities and incidental purposes, recorded August 1, 2003 as Instrument No. 2003-0928641 of Official Records.
In Favor of: San Diego Gas and Electric Company, a corporation
Affects: A portion of said land

The location of the easement cannot be determined from record information.

EXHIBIT B TO AMENDMENT

EXHIBIT F

FORM MEMORANDUM OF LEASE

Recording Requested By:

When Recorded Return To:

LATHAM & WATKINS LLP
Attn: Robert Frances, Esq.
600 West Broadway, 18th Floor
San Diego, California 92101-3375

THE AREA ABOVE IS RESERVED FOR RECORDER'S USE

MEMORANDUM OF LEASE

This Memorandum of Lease ("Memorandum") is made and entered into as of March 30, 2010, by and between BMR-2282 FARADAY AVENUE LLC, a Delaware limited liability company ("Landlord"), and ISIS PHARMACEUTICALS, INC., a Delaware corporation ("Tenant"), in connection with that certain real property located in Carlsbad, California, and more particularly described on **Exhibit "A"** attached hereto and incorporated herein by reference (together with any improvements now or hereafter constructed thereon, the "Premises").

1. Lease. Pursuant to the terms and provisions of that certain unrecorded Lease by and between Landlord and Tenant, dated September 19, 2005, as amended on May 8, 2007 and March 30, 2010 (the "Lease"), Tenant leased the Premises from Landlord. Capitalized terms used herein but not otherwise defined shall have the meanings ascribed thereto in the Lease.

2. Lease Term. The term of the Lease shall commence on September 19, 2005 and end on December 31, 2031, subject to earlier termination of the Lease as provided therein; provided, however, that Tenant shall have four (4) options to extend the Lease term, as further described in Article 36 of the Lease.

3. Purchase Option. The Lease grants Tenant the option to purchase the Premises from Landlord at the end of certain Lease Years:, subject to and in accordance with Section 24.3 of the Lease.

4. Right of First Negotiation. The Lease grants Tenant the right of first negotiation with respect to any sale of the Premises by Landlord to a third party, subject to and in accordance with Section 24.2 of the Lease.

---

5. No Effect on Lease. The parties have prepared, signed, and acknowledged this Memorandum solely for recording purposes. This Memorandum does not modify, increase, decrease, or in any other way affect any party's rights, duties, or obligations under the Lease. Landlord and Tenant each has rights, duties, and obligations (and conditions to its rights) under the Lease but not stated in this Memorandum. If the provisions of the Lease and the provisions of this Memorandum conflict, then the provisions of the Lease shall govern. Nothing in this Memorandum constitutes any representation or warranty by either party. To the extent, if any, that the Lease limits the liability of either Landlord or Tenant, such limitation also applies to any such liability under this Memorandum.

6. Successors and Assigns. The Lease and this Memorandum shall bind and benefit the parties hereto and their successors and assigns.

7. Termination. This Memorandum shall automatically terminate and be of no force or effect upon any termination of the Lease. Within fifteen (15) days following such termination, Tenant will provide to Landlord an executed and acknowledged Quitclaim Deed, releasing and quitclaiming all right, title and interest in and to the Property, specifically including any interest pursuant to the Lease.

8. Counterparts. This Memorandum may be executed in any number of counterparts, each of which shall be deemed to be an original, and all of such counterparts shall constitute one agreement. To facilitate the execution of this Memorandum, the parties may execute and exchange by telephone facsimile or by other electronic methods (including email) counterparts of this Memorandum or the signature pages hereto. Signatures to this Memorandum transmitted electronically or by telecopy shall be valid and effective to bind the party so signing. Each party hereto agrees to promptly deliver to the other party an executed original to this Memorandum with its actual signature, but a failure to do so shall not affect the enforceability of this Memorandum, it being expressly agreed that each party to this Memorandum shall be bound by its own telecopied or electronically delivered signature and shall accept the telecopied or electronically delivered signature of the other parties to this Memorandum.

[Remainder of Page Left Intentionally Blank]

IN WITNESS WHEREOF, Landlord and Tenant have executed this Memorandum of Ground Lease as of the date first above written.

LANDLORD:

BMR-2282 FARADAY AVENUE LLC

By: _____
Name: John Bonanno
Title: Vice President, Development

TENANT:

ISIS PHARMACEUTICALS, INC.

By: _____
Name: B. Lynne Parshall
Title: Chief Operating Officer & Chief Financial Officer

[MEMORANDUM OF LEASE SIGNATURE PAGE]

STATE OF CALIFORNIA }
COUNTY OF } *S.S.*

On , before me, , a Notary Public in and for said County and State, personally appeared,

, who proved to me on the basis of satisfactory evidence to be the person(s) whose name(s) is/are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity(ies), and that by his/her/their signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

I certify under PENALTY OF PERJURY under the laws of the State of California that the foregoing paragraph is true and correct.

WITNESS my hand and official seal.

Signature: _____

(Notary Seal)

[MEMORANDUM OF LEASE ACKNOWLEDGMENT PAGE]

STATE OF CALIFORNIA }
COUNTY OF } *S.S.*

On , before me, , a Notary Public in and for said County and State, personally appeared,

, who proved to me on the basis of satisfactory evidence to be the person(s) whose name(s) is/are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity(ies), and that by his/her/their signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

I certify under PENALTY OF PERJURY under the laws of the State of California that the foregoing paragraph is true and correct.

WITNESS my hand and official seal.

Signature: _____

(Notary Seal)

EXHIBIT "A"

Description of the Property

Real property in the City of Carlsbad, County of San Diego, State of California, described as follows:

Parcel A:

Lot 7 of Carlsbad Tract No. 84-9, according to Map thereof No. 11230, filed in the Office of the County Recorder of San Diego County, May 10, 1985, as instrument no. 85-165947 of Official Records, and a portion of Parcel D of Parcel Map No. 14461, filed in the Office of the County Recorder of San Diego County, September 12, 1986 as instrument no. 86-402406 of Official Records; all in the City of Carlsbad, County of San Diego, State of California, more particularly described as follows:

Commencing at the Northwest corner of said Parcel D of Parcel Map No. 14461; thence along the Westerly property line of said Parcel D, South 18 degrees 26'06" East, 278.43 feet, to the true point of beginning; thence leaving said Westerly line North 50 degrees 30'00" East, 145.33 feet; thence North 70 degrees 12'00" East, 92.23 feet; thence South 39 degrees 30'48" East, 256.97 feet; thence South 50 degrees 29'12" West, 83.13 feet; thence South 71 degrees 33'54" West, 242.68 feet to a point on said Westerly property line; thence North 18 degrees 26'06" West, 215.24 feet to the true point of beginning.

Said property being described as "Parcel C" in a Certificate of Compliance recorded on April 21, 2003 as instrument no. 2003-0459192 of Official Records of said San Diego County.

Parcel B:

A non-exclusive easement on, over and under the common areas as defined and shown on those certain amended and restated declaration of establishment of Covenants, Conditions and Restrictions, and Reservation of Easements (the "Declarations"), dated June 28, 1988 and recorded August 8, 1988 as instrument no. 88-387705 of Official Records, for the purposes of ingress and egress, parking, the construction, installation, maintenance, removal replacements, operation and use of utilities, including but not limited to sewers, water and gas pipes, drainage lines and systems, electric power, conduit lines and wiring, telephone, conduits, lines and wires and other utilities, public or private, beneath the ground surface (except vaults, vents, access, structures and other facilities required to be above ground), subject to the terms, as more particularly set forth in the Declaration.

APN: 212-061-33-00

[MEMORANDUM OF LEASE ACKNOWLEDGMENT PAGE]

CONFIDENTIAL
Execution Copy

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R §§ 200.80(b)4, AND 240.24b-2

RESEARCH, DEVELOPMENT AND LICENSE AGREEMENT

BETWEEN

ISIS PHARMACEUTICALS, INC.,

AND

GLAXO GROUP LIMITED

RESEARCH, DEVELOPMENT AND LICENSE AGREEMENT

This RESEARCH, DEVELOPMENT AND LICENSE AGREEMENT (together with all Appendices and Schedules hereto, the "***Agreement***") is entered into as of the 30th day of March, 2010 (the "***Effective Date***") by and between **ISIS PHARMACEUTICALS, INC.**, a Delaware corporation, having its principal place of business at 1896 Rutherford Road, Carlsbad, CA 92008 ("***Isis***"), and **GLAXO GROUP LIMITED**, a company existing under the laws of England and Wales, having its registered office at Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex, UB6 0NN, England ("***GSK***"). GSK and Isis each may be referred to herein individually as a "***Party***" or collectively as the "***Parties***." The terms used in this Agreement with initial letters capitalized, whether used in the singular or the plural, will have the meaning set forth in APPENDIX 1.

RECITALS

WHEREAS, Isis is the acknowledged leader in the field of Antisense and possesses certain Patent Rights, Know-How and technology with respect to Antisense therapeutics, and has novel and valuable capabilities for the research, discovery, identification, synthesis and development of Antisense therapeutics;

WHEREAS, GSK possesses expertise in the pharmaceutical research, development, manufacturing and commercialization of human pharmaceuticals, and GSK is interested in developing Antisense therapeutics as drug products;

WHEREAS, GSK desires (y) Isis to conduct Collaboration Programs to discover, research and develop Compounds through completion of a Phase 2 PoC Trial, and (z) to have exclusive options, exercisable at or prior to completion of a Phase 2 PoC Trial, to further Develop and Commercialize such Collaboration Programs; and

WHEREAS, upon GSK's exercise of any of its options to such Collaboration Programs, GSK will obtain an exclusive license under this Agreement to Develop and Commercialize Licensed Products.

NOW, THEREFORE, in consideration of the respective covenants, representations, warranties and agreements set forth herein, the Parties hereto agree as follows:

ARTICLE 1.
COLLABORATION PROGRAMS

1.1. **Overview.** The intent of the Collaboration is for Isis to continue to independently (i) conduct Collaboration Programs to generate at least one (1) Development Candidate and, subject to Section 1.4.4(a) regarding [***], one (1) Back-Up Compound for each Collaboration Program; and (ii) advance each Development Candidate through the completion of the first Phase 2 PoC Trial under the applicable Collaboration Program, with respect to which Collaboration Program GSK may exercise its option to further Develop and ultimately Commercialize such Collaboration Program through Licensed Products under an exclusive license from Isis (the "***Objective***"). Isis will be responsible to progress each Collaboration Program through completion of a Phase 2 PoC

Trial. For each Collaboration Program, GSK will have an option (exercisable on or before the completion of the first Phase 2 PoC Trial) to obtain from Isis an exclusive license to Develop and Commercialize the Licensed Compounds and Licensed Products under such Collaboration Program. The purpose of this Section 1.1 is to provide a high-level overview of the roles, responsibilities, rights and obligations of each Party under this Agreement, and therefore this Section 1.1 is qualified in its entirety by the more detailed provisions of this Agreement set forth below.

1.2. **Collaboration Term**. Subject to Section 1.8, the term for the conduct of Collaboration Programs (the "***Collaboration Term***") will begin on the Effective Date and end on the [***] ([***]) anniversary of the Effective Date.

1.3. **Collaboration Management**.

1.3.1. **JSC**. The Parties will establish a joint steering committee (the "***JSC***") to provide advice and make recommendations on how to conduct the Collaboration. The JSC will consist of three (3) representatives appointed by Isis and three (3) representatives appointed by GSK. Each Party will designate one of its three (3) representatives who possesses a thorough understanding of the scientific and business issues relevant to this Agreement to act as the co-chair of the JSC. The co-chairs will be responsible for ensuring that activities occur as set forth in this Agreement, including ensuring that the JSC meetings occur, material recommendations of the JSC are properly reflected in the minutes, and any dispute is given prompt attention and resolved in accordance with Sections 1.3.3 and 12.1.

(a) The JSC operating procedures, including but not limited to frequency of meetings (at least quarterly), location of meetings, and responsibilities for agendas and minutes, will be determined by the JSC. The JSC will codify these operating procedures in the written minutes of the first meeting.

(b) The JSC may hold quarterly meetings in person or by audio or video conference as determined by the JSC and will hold meetings as necessary under Section 1.5; but at least two (2) meetings per year will be in person (one held at Isis' facilities, and the other held at GSK's U.S. facilities). Alliance Managers will attend JSC meetings as participating non-members. In addition, upon prior approval of the other Party each Party may invite its employees or consultants to attend JSC meetings, including, without limitation, any subject matter expert(s) with valuable knowledge of a specific Collaboration Target, disease, or Indication that is the subject of a Collaboration Program.

(c) The JSC members from the same Party will collectively have one (1) vote. The JSC will strive to make recommendations with approval of both Isis members and GSK members, and record such recommendations in the minutes of the applicable JSC meeting.

(d) Each Party will be responsible for the costs and expenses of its own JSC members.

1.3.2. **Role of the JSC**. Without limiting any of the foregoing, subject to Section 1.3.3, the JSC will perform the following functions, some or all of which may be addressed directly at any given meeting of the JSC:

(a) review progress on improvements to Antisense technology and advances in mechanistic understandings of Antisense technology;

(b) review and provide advice on the Collaboration Program Research Plan (defined below) for each Collaboration Program, and the Early Development Plan (defined below) for each Development Candidate;

(c) review the overall progress of Isis' efforts to achieve Sanctioned Target status with respect to each Collaboration Program that has not achieved Sanctioned Target status;

(d) review the overall progress of Isis' efforts to discover, identify, optimize and otherwise Develop Compounds under each Collaboration Program;

(e) review and approve new gene targets for substituting any Unvalidated Collaboration Program and determine whether the new Collaboration Targets are primarily associated with a Rare Disease in accordance with Section 1.5.2;

(f) review and provide advice on (i) design and content of the [***] for each Collaboration Program and (ii) the [***] for each Collaboration Program, with each of (i) and (ii) being subject to [***] as described in Section 1.3.3; and

(g) such other review and advisory responsibilities as may be assigned to the JSC pursuant to this Agreement or as may be mutually agreed upon in writing by the Parties from time to time.

1.3.3. **Decision Making**. The Parties will conduct the Collaboration giving due consideration to the recommendations and advice of the JSC. Isis will have the final decision-making authority regarding [***], subject to compliance with the Collaboration Program Research Plan (where applicable) and the terms of this Agreement. GSK will have the final decision-making authority (i) with respect to any [***], any disputes concerning the interpretation and application of the [***], which [***] is set forth in [***], and the establishment of the [***]; and (ii) with respect to any [***], any disputes concerning the interpretation and application of the [***], which [***] is set forth in [***] and the establishment of the [***]. Notwithstanding anything in this Agreement to the contrary, the [***] and the [***] for the applicable Collaboration Programs will at all times be documented in APPENDIX 8(A) or APPENDIX 8(B), as applicable, and APPENDIX 8(A) and APPENDIX 8(B) may only be modified as mutually agreed in writing by both GSK and Isis. Notwithstanding the foregoing, the approval of a new gene target for substituting an Unvalidated Collaboration Program in accordance with Section 1.5.2 and the determination of whether In Vivo Efficacy has been demonstrated require mutual consent of the Parties and if the Parties cannot reach such mutual consent, the Parties will resolve such dispute by submitting the matter to an Expert Panel pursuant to Section 12.1.3.

1.3.4. **Term of the JSC.** The JSC (and any of its subcommittees and working groups) as a formal governing body under this Agreement will be dissolved upon the later of (i) the expiration of the Collaboration Term and (ii) the exercise or expiration of the Option with respect to the last Collaboration Program.

1.3.5. **Alliance Managers.** Each Party will appoint one representative who possesses a general understanding of the scientific and business issues relevant to this Agreement to act as its alliance manager (each, an "***Alliance Manager***") under this Agreement. Each Alliance Manager will be responsible for performing the Alliance Management Activities.

1.3.6. **IDJSC.** The Parties will also establish a joint steering committee to provide advice and make recommendations on how to conduct the ID/Additional Programs (the "***IDJSC***"). The IDJSC will consist of three (3) representatives appointed by Isis and three (3) representatives appointed by GSK. Each Party will designate one of its three (3) representatives who possesses a thorough understanding of the scientific and business issues relevant to infectious diseases to act as the co-chair of the IDJSC. The co-chairs will be responsible for ensuring that activities occur as set forth in this Agreement with respect to the ID/Additional Programs, including ensuring that the IDJSC meetings occur, and material recommendations of the IDJSC are properly reflected in the minutes. The IDJSC will operate in accordance with the same operating procedures for the JSC as set forth in Section 1.3.1. The IDJSC members from the same Party will collectively have one

(1) vote. The IDJSC will strive to make recommendations with approval of both Isis members and GSK members, and record such recommendations in the minutes of the applicable IDJSC meeting. Any dispute with respect to the ID/Additional Programs that cannot be resolved by the IDJSC shall be submitted to the JSC and JSC shall resolve such dispute in accordance with Sections 1.3.3 and 12.1. With respect to the ID/Additional Programs, unless the context otherwise requires, a reference in this Agreement to the "*JSC*" will be a reference to the "*IDJSC*."

1.3.7. **Role of the IDJSC**. Subject to Section 1.3.3 and solely in connection with the ID/Additional Programs, the IDJSC will perform the following functions, some or all of which may be addressed directly at any given meeting of the IDJSC:

(a) review progress on improvements to Antisense technology and advances in mechanistic understandings of Antisense technology;

(b) review and provide advice on the Collaboration Program Research Plan for each ID/Additional Program, and the Early Development Plan for each Development Candidate under the ID/Additional Programs;

(c) review the overall progress of Isis' efforts to achieve Sanctioned Target status with respect to each ID/Additional Program;

(d) review the overall progress of Isis' efforts to discover, identify, optimize and otherwise Develop Compounds under each ID/Additional Program;

(e) determine criteria for achieving In Vivo Efficacy for the 6th Collaboration Program, if any, within sixty (60) days following selection;

(f) discuss and approve the design and expenditure for animal efficacy studies;

(g) review and determine whether In Vivo Efficacy has been demonstrated under the ID/Additional Programs;

(h) subject to [***] as described in Section 1.3.3, review and provide advice on (i) design and content of the [***] and the [***] for each ID/Additional Program and (ii) the [***] and [***] for each ID/Additional Program, including [***]; and

(i) such other review and advisory responsibilities as may be assigned to the IDJSC pursuant to this Agreement or as may be mutually agreed upon in writing by the Parties from time to time.

1.3.8. **Term of IDJSC.** The IDJSC (and any of its subcommittees and working groups) as a formal governing body under this Agreement will be dissolved upon the later of (i) the expiration of the Collaboration Term and (ii) the exercise or expiration of the Option with respect to the last ID/Additional Program.

1.3.9. **ID Alliance Managers.** Each Party will appoint one representative who possesses a general understanding of the scientific and business issues relevant to infectious diseases to act as its Alliance Manager with respect to the ID/Additional Programs. Such Alliance Manager will be responsible for performing the Alliance Management Activities solely with respect to the ID/Additional Programs.

1.3.10. **Meeting Coordination.** Isis and GSK will schedule meetings of the JSC and IDJSC to take place at the same location and on the same dates to maximize the use of each Party's time, increase information sharing efficiencies and reduce the cost of additional travel, lodging and related expenses.

1.4. **Isis' Collaboration Responsibilities**.

1.4.1. **(a)** **Collaboration Programs**. Subject to and in accordance with the terms of this Agreement, Isis will be responsible for conducting five (5) Collaboration Programs, each to be focused on a different Collaboration Target; *provided, however*, that GSK may add a sixth (6^{th}) Collaboration Program for Isis to conduct under this Agreement by notifying Isis in writing of its intention to add the sixth (6^{th}) Collaboration Program on or before the [***] ([***]) anniversary of the Effective Date and paying Isis a fee of $[***] within thirty (30) days after the final selection of the sixth (6^{th}) Collaboration Target pursuant to Section 1.5.1. A brief description of the initial five (5) Collaboration Programs, including the applicable Collaboration Targets (and whether such Collaboration Programs are Rare Disease Programs, [***] Program or ID/Additional Programs), is set forth on APPENDIX 5, attached hereto.

(b) **Isis Diligence**. Isis will use Commercially Reasonable Efforts, subject to Section 1.6, to conduct (i) drug discovery activities including drug screening, identification, characterization, optimization and other necessary activities according to the applicable Collaboration Program Research Plans, and (ii) drug development of each Development Candidate under a Collaboration Program in accordance with the applicable Early Development Plan. To that end, Isis will dedicate to the

conduct of the activities hereunder the appropriate resources and allocate personnel with an appropriate level of education, experience and training reasonably necessary to achieve the Objective efficiently and expeditiously, which will at a minimum be the capacity with which Isis runs its drug discovery efforts for similar programs as of the Effective Date.

(c) **Collaboration Program Research Plans; Early Development Plans.** Isis will carry out its drug discovery efforts for each Collaboration Program pursuant to the applicable Collaboration Program Research Plan; and its drug development efforts for each Development Candidate pursuant to an Early Development Plan, in each case subject to Section 1.6 and Section 1.7, and review and comment by the JSC as described in Section 1.3.2(b). Isis will update each Collaboration Program Research Plan and Early Development Plan as needed, but at least once annually, and submit it to the JSC for its review and comment, subject to [***] as

described in Section 1.3.3 on the [***] and the [***] for all Collaboration Programs, and for ID/Additional Programs, the [***] and the [***], as applicable.

For each Collaboration Program, and each Development Candidate, as applicable, Isis will provide the JSC:

(i) promptly (but no later than ninety (90) days) following the Effective Date (or, with respect to the sixth (6^{th}) Collaboration Program or any Collaboration Program for a substituted target, within ninety (90) days after its designation) for each Collaboration Program that has not reached [***];

(ii) the [***] approved by Isis' RMC for each [***], as may be modified from time to time to address the [***] and [***] activities Isis will conduct under the Collaboration for such [***] (each such plan under Sections 1.4.1(c)(i) and 1.4.1(c)(ii), a "***Collaboration Program Research Plan***"); and

(iii) (A) for each [***] under a Collaboration Program for Rare Diseases or [***], an [***] that will first consist of the [***] approved by Isis' DMC following designation of the applicable [***] by Isis' RMC, and thereafter Isis will update as the program advances to include an initial [***], and once GSK provides the [***], a [***]; and (B) for each [***] under an ID/Additional Program, an initial [***] that will first consist of the [***] approved by Isis' DMC following designation of the applicable [***] by Isis' RMC, and thereafter Isis will update as the program advances to include the [***] provided by GSK; and once GSK provides the [***], a [***] (each such plan, an "***Early Development Plan***"), in all cases taking into consideration the recommendations of the JSC or IDJSC as described in Section 1.3.2(b) and Section 1.3.7(b), as applicable.

(d) **Briefing the JSC.** At each regularly scheduled meeting of the JSC, Isis will provide to the JSC (i) progress updates on the status of the Collaboration generally; (ii) progress updates of Collaboration Program Research Plans; and (iii) progress updates of Early Development Plans for each Development Candidate, in each case, together with a summary of data associated with Isis' research and/or Development activities for each Collaboration Program.

1.4.2. **Drug Discovery.** Isis will use Commercially Reasonable Efforts to apply Antisense technology to and otherwise conduct the following Collaboration drug discovery research activities, in each case consistent with the level of quality, effort, resources and diligence Isis applies to its other internal and partnered programs:

(a) conduct early-stage drug discovery on each Collaboration Program that has not achieved Sanctioned Target status;

(b) conduct late-stage drug discovery on each Collaboration Program that has achieved Sanctioned Target status with the goals of identifying one (1) lead compound that would qualify as a Development Candidate and, subject to Section 1.4.4(a) regarding [***], at least one (1) Back-Up Compound in each Collaboration Program; and

(c) each time a Development Candidate is designated under a Collaboration Program, Isis will notify GSK in writing within thirty (30) days of such designation and will provide GSK (i) the [***] Isis provided to its RMC and the JSC in connection with Isis' designation of the applicable Compound as a Development Candidate, (ii) a proposed Early Development Plan with respect to such Development Candidate, (iii) a summary of the [***] and, to the best of Isis' knowledge and belief, the need to [***], and (iv) a description of any [***] applicable to such Development Candidate (such notice and package, a "***Development Candidate Package***").

1.4.3. **Drug Development.** Isis will use Commercially Reasonable Efforts to conduct the following drug development activities under this Agreement:

(a) Subject to Section 1.6 and Section 1.7 below, for each Collaboration Program, Develop at least one (1) Development Candidate through the completion of the first Phase 2 PoC Trial; *provided, however,* Isis may discontinue such Development if at any time (i) Isis in good faith believes, and a majority of the JSC recommends, that continuing such Development is not warranted because the Development Candidate has not demonstrated sufficient efficacy or activity in human trials or animal studies, or (ii) after having consulted the JSC, Isis in good faith believes that continuing such Development would (x) pose an unacceptable risk or threat of harm in humans, or (y) violate any Applicable Law, ethical principles, or principles of scientific integrity; *provided, further*, that Isis will [***] the expiration or termination of the Collaboration Term;

(b) ***Phase 1 Trial Design.*** For any Phase 1 Trial conducted by Isis for a Collaboration Program, which Phase 1 Trial may include patients as well as healthy volunteers, Isis will include a [***] when feasible and appropriate for the Development Candidate; *provided that* for ID/Additional Programs, [***], including that the total number of healthy subjects and patients in Phase 1 and Phase 2 PoC Trials shall be [***]. Isis acknowledges that for the ID/Additional Programs, unless otherwise agreed by GSK and Isis in APPENDIX 8(B), [***], and Isis shall conduct such [***], prior to commencement of the [***]; and

(c) ***Phase 2 PoC Trial.*** Each Phase 2 PoC Trial shall be designed in accordance with the [***] for Collaboration Programs for Rare Diseases and [***], and [***] for ID/Additional Programs. No later than [***] days prior to the anticipated commencement date of a Phase 2 PoC Trial, Isis will provide GSK with an [***] for the Phase 2 PoC Trial, and GSK will have the right to provide input regarding [***] for such Phase 2 PoC Trial. Isis will keep GSK informed of the progress and status of each Phase 2 PoC Trial and will provide GSK with the applicable Phase 2 PoC Data Package upon completion of such Phase 2 PoC Trial.

1.4.4. **Development of Back-Up Compounds**.

(a) Prior to GSK's exercise of an Option with respect to the Collaboration Program, Isis will use Commercially Reasonable Efforts to develop the Back-Up Compound to Development Candidate status in addition to the lead Development Candidate, at no additional cost to GSK; *provided, however,* the Parties acknowledge [***] presents a significant challenge for the identification of Back-Up Compounds and, as such, it may be commercially reasonable to [***], as the case may be, Development of any Back-Up Compounds for any Collaboration Program focused on a [***].

(b) In addition, if, prior to the date GSK exercises the applicable Option, GSK or the JSC reasonably determines that a Development Candidate [***] or has otherwise [***] Trial [***], Isis will Develop the Back-Up Compound for such Collaboration Program through completion of a Phase 2 PoC Trial in accordance with this Agreement as long as the Parties and the JSC share a reasonable belief that such Back-Up Compound has properties that are likely to make it successful in Development and Commercialization. [***] will be responsible for the costs and expenses to Develop such Back-Up Compound in accordance [***].

(c) Notwithstanding the provisions of Section 1.4.4(a), but subject to the proviso in Section 1.4.4(a) regarding [***], at any time before or after GSK exercises an Option for a given Collaboration Program, upon written request from GSK, Isis will commence further Development work on a Back-Up Compound beyond Development Candidate status in the same manner as Isis would develop a Development Candidate under Section 1.4.3. Isis will perform such Development work contemporaneously with the Development Isis is conducting on the Development Candidate under the applicable Collaboration Program and in accordance with a budget approved by GSK. [***] will be responsible for the costs and expenses to further Develop such Back-Up Compound in accordance [***].

1.4.5. **Follow-On Compounds.** After GSK has [***], if GSK wants Isis to discover and develop a Follow-On Compound for the applicable Licensed Product/Collaboration Program, then GSK will provide a written request to Isis. Upon Isis' receipt of such request, Isis will commence drug discovery efforts to identify a Follow-On Compound against the same Collaboration Target within the applicable Collaboration Program, and use Commercially Reasonable Efforts to develop such Follow-On Compound to the Development Candidate stage [***]. Once a Follow-On Compound is designated as a Development Candidate in accordance with this Agreement, GSK is solely responsible, [***], for Developing and

Commercializing such Follow-On Compound. So long as GSK has exercised the applicable Option and is compliant with the terms of this Agreement with respect to such Follow-On Compound, such Follow-On Compound will be considered a Licensed Product under this Agreement. Notwithstanding the foregoing, Isis will not be required to discover or Develop a Follow-On Compound for any Collaboration Program focused on a [***]. The Party responsible for the costs and expenses to Develop such Follow-On Compounds will be determined in accordance with Section 1.7.4.

1.4.6. **Data Integrity**.

(a) Isis acknowledges the importance to GSK of ensuring that the activities under Collaboration Programs are undertaken in accordance with the following good data management practices ("***Good Data Management Practices***"):

(i) data are being generated using sound scientific techniques and processes;

(ii) data are being accurately recorded in accordance with good scientific practices by persons conducting research hereunder;

(iii) data are being analyzed appropriately without bias in accordance with good scientific practices;

(iv) data and results are being stored securely and can be easily retrieved, and

(v) where, pursuant to then-existing policies and procedures, Isis' senior management documents in writing its key decisions, it will follow its internal procedures and policy, so as to demonstrate and/or reconstruct key decisions made by such senior management during the conduct of the research and Development activities under this Agreement.

(b) Isis agrees that it will carry out the activities under the Collaboration Programs and collect and record any data generated therefrom in a manner consistent with the above requirements, and will, upon reasonable request by GSK, permit review of relevant notebooks and records by GSK during normal business hours.

1.4.7. **Isis Technology.** In performing its research and development responsibilities under this Agreement, Isis will utilize any next generation Antisense chemistries and oligonucleotides Controlled by Isis or its Affiliates, using traditional and novel mechanisms of action, including, but not limited to, [***], as recommended by the JSC. Except as otherwise set forth in this Agreement, Isis' use of any and all improvements that are Controlled by Isis or its Affiliates to its Antisense chemistries or oligonucleotide motifs in the Collaboration Programs [***].

1.5. **Adding Sixth (6th) Collaboration Program; Limited Right to Substitute Collaboration Programs**.

1.5.1. **Selecting Sixth (6th) Collaboration Program (if any)**. If GSK elects to add a sixth (6th) Collaboration Program under Section 1.4.1(a), then within thirty (30) days of GSK's notice

electing such addition, GSK will provide Isis a gene target for consideration to be the focus of the sixth (6th) Collaboration Program, including the gene name and the NCBI accession number or nucleic acid sequence for such proposed target. Together with GSK, Isis will

review and evaluate if, at the time of such request, [***] for such proposed gene target; [***] Isis has [***] under this Agreement for such program [***]; and [***] Isis [***] the program proposed by GSK [***] collectively, the "***Collaboration Target Acceptance Criteria***"). If, at such time, the proposed gene target fails to meet the Collaboration Target Acceptance Criteria, the proposed gene target will be rejected and will not become the focus of the sixth (6th) Collaboration Program. If the proposed gene target is rejected, GSK may request another gene target in accordance with the terms of this Section 1.5.1. If the proposed gene target is not rejected, such proposed gene target will be the sixth (6th) Collaboration Target. Isis will not directly or indirectly research, develop or commercialize any Compounds with respect to any gene target rejected under this Section 1.5.1 if such gene target is rejected as a result of [***]. For purposes of this Section 1.5.1 and the sixth (6th) Collaboration Program, if the relevant gene target is an infectious agent, then the gene target shall be deemed the entire infectious agent and not a specific gene of the infectious agent.

1.5.2. **Limited Right of Substitution**. If, by the [***] ([***]) anniversary of the Effective Date, a Rare Disease Program or a [***] Program has not reached the Sanctioned Target stage (each such program, an "***Unvalidated Collaboration Program***"), then within thirty (30) days following such [***] ([***]) anniversary, GSK will notify Isis whether GSK wishes (i) Isis to continue its research and development activities under this Agreement for such Unvalidated Collaboration Program; or (ii) subject to the procedures set forth below, to substitute a new program for such Unvalidated Collaboration Program; *provided* GSK may only substitute up to a total of [***] ([***]) Unvalidated Collaboration Programs (and for purposes of clarity, may not substitute any [***]). If GSK timely elects to substitute an Unvalidated Collaboration Program under this Section 1.5.2, then GSK will propose a list of new gene targets for consideration as part of the substituted Collaboration Program, by adding such gene targets (including the gene name and the NCBI accession number or nucleic acid sequence for the proposed gene target and whether GSK believes such gene target is primarily associated with a Rare Disease) to the written agenda for the next scheduled JSC meeting; *provided* GSK must make such proposal at least fifteen (15) Business Days prior to such JSC meeting. GSK may call an emergency JSC meeting for such purpose. At such JSC meeting, the representatives of Isis and GSK will (i) mutually agree upon the replacement Collaboration Program(s) based on the greatest likelihood of success and using the same process as set forth in Section 1.5.1 above, and (ii) determine whether the applicable Collaboration Targets that are the focus of such Collaboration Programs are primarily associated with a Rare Disease. With respect to any Collaboration Program substituted in under this Section 1.5.2 where the Parties agree the applicable Collaboration Target is primarily associated with a Rare Disease, then, for purposes of calculating the applicable payments under ARTICLE 5 of this Agreement, the Collaboration Program associated with such Collaboration Target will be treated as a Rare Disease Program. With respect to any Collaboration Program substituted in under this Section 1.5.2 where the Parties agree the applicable Collaboration Target is *not* primarily associated with a Rare Disease, then, for purposes of calculating the applicable payments under ARTICLE 5 of this Agreement, the Collaboration Program associated with such

Collaboration Target will be treated as a [***] Program. If, within thirty (30) days following such JSC meeting, the Parties cannot agree whether the applicable Collaboration Target is primarily associated with a Rare Disease, the Parties will resolve such dispute by submitting the matter to an Expert Panel pursuant to Section 12.1.3. Any Unvalidated Collaboration Program that GSK elects to substitute out under this Section 1.5.2 will no longer be a Collaboration Program under this Agreement and the applicable gene target associated therewith will no longer be a Collaboration Target under this Agreement. Isis' obligations (including but not limited to ARTICLE 1 and ARTICLE 2) and GSK's rights and Options under this Agreement with respect to such substituted out gene targets and Compounds directed against such gene targets will terminate. As of the Effective Date, the Collaboration Program focused on [***] and the Collaboration Program focused on [***] have each reached the [***] stage. Isis will not directly or indirectly research, develop or commercialize any Compounds with respect to any gene target rejected pursuant to this Section 1.5.2 if such gene target is rejected as a result of Clause (A) set forth in the Collaboration Target Acceptance Criteria without providing GSK during the Collaboration Term with [***].

1.6. **[***]Special Conditions of [***] and [***] Programs**.

1.6.1. **[***] Program**

(a) **[***]**. Isis will use Commercially Reasonable Efforts to conduct drug discovery activities including drug screening, identification, characterization, optimization and other necessary activities according to the applicable Collaboration Program Research Plans for each [***], with the goal of reaching the Sanction Target stage for each [***]. Isis' drug discovery and development programs on each [***] will be considered a separate and distinct Collaboration Program under this Agreement and the [***] ([***]) [***] will only count as a single Collaboration Program against the limit on the maximum number of Collaboration Programs set forth in Section 1.4.1(a). Each time Isis designates a [***] as a Sanctioned Target, Isis will notify GSK in writing within thirty (30) days of such designation and will provide GSK (a) the same [***] Isis provided its RMC and the JSC in connection with Isis' decision to designate such [***] as a Sanctioned Target, (b) a proposed [***] with respect to such [***], (c) a summary of the [***] and, to the best of Isis' knowledge and belief, the need to [***] any [***], and (d) a description of any [***] applicable to such [***] (such notice and package, a "***[***] Sanction Notice***"). GSK will then have ninety (90) days following its receipt of the applicable [***] Sanction Notice (each, a "***[***] Election Deadline***") to notify Isis whether GSK elects to maintain such [***] as a Collaboration Program. If GSK delivers a written notice to Isis that affirmatively elects to maintain the applicable [***] as a Collaboration Program before the applicable [***] Election Deadline, then Isis' drug discovery program focused on such [***] will remain a Collaboration Program under this Agreement, and Isis will perform the applicable research and development activities set forth in Section 1.4 above. If GSK does not deliver a written notice to Isis that affirmatively elects to maintain the applicable [***] as a Collaboration Program before the applicable [***] Election Deadline, or if GSK delivers a notice indicating that GSK does not wish to maintain the

applicable [***] as a Collaboration Program, then, in each case, (i) Isis will no longer be required to perform any work on such [***] under this Agreement, and (ii) such [***] will no longer be considered a Collaboration Target or part of a Collaboration Program. For clarity, if a [***] is no longer a Collaboration Target but another [***] continues to be part of a Collaboration Program, GSK will not have a replacement right under Section 1.5.2 above with respect to the discontinued [***]. In addition, following delivery of the applicable [***] Sanction Notice, if GSK elects to maintain the [***] ([***]) [***] as a Collaboration

Program under this Section 1.6.1, then within sixty (60) days after receipt by GSK of an invoice (sent from Isis on or after the date GSK makes the applicable election), GSK will pay a fee of $[***] for such [***] election (i.e., [***] Collaboration Programs will require [***] $[***] payment and no additional payment if GSK elects to have only [***] ([***]) [***] Collaboration Program) under this Section 1.6.1.

(b) **Right of First Negotiation with Respect to [***]**. If, during the Collaboration Term, Isis (a) has a good-faith desire to grant any Third Party any right with respect to [***] or collaborate with any Third Party in researching, developing or commercializing Compounds with respect to [***] or (b) Initiates a Phase 2 PoC Trial for a Compound with respect to [***], then Isis will promptly (but in any case within thirty (30) days) provide written notice to GSK, and Isis will promptly deliver to GSK evaluation materials reasonably relevant to its [***] program and no less than those materials provided to applicable Third Parties, including a proposed collaboration plan, if any, and all information about the Compounds with respect to [***] consistent with the information Isis is required to disclose as part of a Phase 2 PoC Data Package, if any. GSK will then have forty-five (45) days to notify Isis in writing whether GSK desires to collaborate with Isis in researching, Developing or Commercializing Compounds with respect to [***]. If GSK provides Isis with timely written notice that GSK desires to collaborate with Isis in researching, Developing or Commercializing Compounds with respect to [***] (including obtaining an exclusive license), then Isis and GSK will, in good faith, use commercially reasonable efforts to conclude a written collaboration and license agreement within [***]([***]) days. If GSK fails to timely notify Isis that GSK desires to collaborate and obtain an exclusive license with respect to the [***] program, or if despite good-faith commercially reasonable efforts GSK and Isis are unable to reach an agreement within [***] ([***]) days after Isis' receipt of such notice from GSK, then Isis may enter into a collaboration and license agreement with any Third Party with respect to [***]. For the avoidance of doubt, the right of first negotiation described herein will (x) not prevent Isis from researching or developing the applicable gene target, Compound or Development Candidate for itself through the use of Third-Party contract research organizations and other Third Parties performing similar fee-for-service drug research and development services for or on behalf of Isis; and (y) expire upon the [***], and will only be extended beyond the [***] if and to the extent GSK has the right to notify Isis in writing within the forty-five (45) day period described above and, if such notice is timely delivered by GSK, to the extent Isis and GSK are negotiating in good faith to conclude a written collaboration and license agreement within the [***] ([***]) day period described above.

1.6.2. **[***] Programs**.

(a) **Prior to Sanctioned Target Status**. With respect to the [***] Program, initially Isis will perform the drug discovery and Development activities under this Agreement for [***] and in a [***] using the same Compounds for the treatment of [***] via [***] and [***] with the goal of reaching the Sanctioned Target stage; *provided*, *however*, that, as part of such [***] Program, GSK may, at its sole cost and subject to Section 1.9.2, conduct or have conducted drug discovery activities with such Compounds for [***] using other [***] available to GSK, pursuant to mutually agreed protocols.

(b) **Initial Election; [***] Field**. Once Isis designates [***] as a Sanctioned Target, Isis will notify GSK in writing within thirty (30) days of such designation and will provide GSK (i) the same [***] Isis provided its RMC and the JSC in connection with Isis' decision to designate [***] as a Sanctioned Target, (ii) a proposed [***] with respect to [***] in both the field of [***] and [***], (iii) a summary of the [***] and, to the best of Isis' knowledge and belief, the need to [***] any [***]; and (iv) a description of any [***] applicable to [***] (such notice and package, a "***[***] Notice***"). GSK will then have ninety (90) days following its receipt of the [***] Notice (the "***First [***] Election Deadline***") to notify Isis whether GSK elects to continue the [***] Program in the field of [***], in the field of [***], or in both the fields of [***] and [***] using the same Compounds for treating [***]. If GSK elects to continue with only one field, then the field in which GSK elects to continue the [***] Program under this Section 1.6.2(b) will be considered the "***Base [***] Field***" and the field in which GSK does not elect to continue will be considered the "***Expanded [***] Field***." If GSK does not elect either [***] or [***] by the First [***] Election Deadline, then the Base [***] Field will be considered [***], and the Expanded [***] Field will be considered [***]. Isis will perform the drug discovery and Development activities in accordance with this Agreement, including but not limited to Section 1.4, in the Base [***] Field (the "***Base [***] Program***") and the Expanded [***] Field if GSK elects to have Isis perform the drug discovery and Development activities in the Expanded [***] Field (the "***Expanded [***] Program***").

(c) **Subsequent Option to Expand**. At any time from the First [***] Election Deadline through the date of the first Option Deadline under Section 3.1 for the [***] Program (the "***Final [***] Election Deadline***"), GSK may elect to have Isis perform the Expanded [***] Program either (i) using the same Compound Isis is Developing under the Base [***] Program (such program, the "***Same Compound-Expanded [***] Program***"), or (ii) using a different Compound than the Compound Isis is Developing under the Base [***] Program (such program, the "***Different Compound-Expanded [***] Program***"). GSK will make any election under this Section 1.6.2, by providing written notice to Isis, or specifically making such election at a JSC meeting where such election is documented in the minutes of the applicable meeting. Within sixty (60) days after GSK notifies Isis of its desire to expand the [***] Program, Isis shall provide GSK with (i) a [***] summarizing the [***] of the Base [***] Program; (ii) a proposed [***] or [***] with respect to

the Expanded [***] Program; (iii) a summary of the [***] and, to the best of Isis' knowledge and belief, the need to [***] any [***] (iv) a description of any [***] applicable to the Expanded [***] Program; and (v) all other information that is useful to GSK's election to expand the Base [***] Program (the "***[***] Data Package***"). If GSK elects to expand the [***] Program to include the Expanded [***] Program, the Base [***] Program and such Expanded [***] Program will only count as a single Collaboration Program against the limit on the maximum number of Collaboration Programs set forth in Section 1.4.1(a). If GSK does not provide Isis with a written notice electing to expand the [***] Program in accordance with this Section 1.6.2 prior to the expiration of the Final [***] Election Deadline, Isis shall have no obligation to conduct the [***] Program in the Expanded [***] Field, the Expanded [***] Field will not be considered a Collaboration Program under this Agreement.

(d) **Electing the Same Compound-Expanded [***] Program at or Before [***]**. If GSK elects the Same Compound-Expanded [***] Program at or before [***]:

(i) Within thirty (30) days, the JSC will meet and prepare a research or Development plan for advancing such Expanded [***] Program to the next stage.

(ii) Isis will provide a good-faith estimate of the costs (including external costs, internal costs and FTEs) to advance the Same Compound-Expanded [***] Program to the next stage based on the JSC's research or Development plan, as well as a good-faith estimate of the costs (including external costs, internal costs and FTEs) to advance the Base [***] Program to the next stage based on the existing Collaboration Program Research Plan or Collaboration Program Development Plan, as the case may be, for the Base [***] Program. Isis' estimate of such costs shall be subject to GSK's approval; *provided, however*, that Isis has no obligation to conduct the Same Compound-Expanded [***] Program unless and until GSK approves such costs and pays Isis the milestones set forth in Section 1.6.2(d)(iii) below.

(iii) After GSK's approval of the estimated costs described in Section 1.6.2(d)(ii) above, GSK will make milestone payments to Isis equal to [***] (including [***]) to advance the Same Compound-Expanded [***] Program to the next Development stage *minus* the [***] [***] to advance the Base [***] Program to the same Development stage (such [***], the "***[***]***") as follows:

(A) within thirty (30) days after reaching the [***] stage, the [***] for developing the Compound through [***],

(B) within thirty (30) days after the [***], the [***] for developing the Development Candidate through [***],

(C) within thirty (30) days after the [***], the [***] for developing the

Development Candidate from [***] through the [***], and

(D) within thirty (30) days after the [***], the [***] for developing the Development Candidate from [***] through completion of the [***]

(iv) GSK will pay Isis [***] ([***]) Option exercise fee under Section 5.4 for the [***] Program, [***] if GSK exercises its Option for both the Base [***] Program and the Same Compound-Expanded [***] Program under this Section 1.6.2(d). In addition, subject to Section 1.6.2(g) below, GSK will pay (a) the [***] ([***]) [***] payments under [***] of [***] of [***] for any Development Milestone Events achieved by the Base [***] Program after such Option exercise, and (b) the [***] payments under [***] of [***] of [***] for any Development Milestone Events achieved by the Same Compound-Expanded [***] Program after such Option exercise.

(e) **Electing the Same Compound-Expanded [***] Program After [***]**. If GSK elects the Same Compound-Expanded [***] Program after [***] but prior to the expiration of the Final [***] Election Deadline (including re-electing the Same Compound-Expanded [***] Program after it discontinues the Same Compound-Expanded [***] Program that it has elected previously), GSK will pay Isis:

(i) a fee of $[***] within thirty (30) days after GSK's receipt of the updated [***] Data Package from Isis. GSK's election will become effective upon such payment to Isis;

(ii) for each Development Milestone Event achieved by a Compound after [***] but through and including the first [***], GSK will pay [***] to Isis for both the Base [***] Program and the Same Compound-Expanded [***] Program as set forth in [***] of [***] of [***];[***]subject to Section 1.6.2(g) below, for each Development Milestone Event achieved by a Compound after the [***] ([***]) [***] GSK will pay (a) the [***] ([***]) [***] of [***] of [***] for any such Development Milestone Events achieved by the Base [***] Program, and (b) the [***] payments under [***] of [***] of [***] for any such Development Milestone Events achieved by the Same Compound-Expanded [***] Program; and

(iii) only one (1) [***] under [***] for the [***] Program, even if GSK exercises its Option for both the Base [***] Program and the Same Compound-Expanded [***] Program under this Section 1.6.2(e).

(f) **Electing the Different Compound-Expanded [***] Program**. If GSK elects the Different Compound-Expanded [***] Program at any time prior to the expiration of the Final [***] Election Deadline, (i) GSK will pay Isis a fee of $[***] within thirty (30) days after its receipt of the updated [***] Data Package, and GSK's election will only become effective upon such payment to Isis; (ii) GSK will pay [***] ([***]) separate [***] under [***] of [***] of [***] for the Base [***] Program and the Different Compound-Expanded [***] Program if GSK exercises its Option for both such programs; and (iii) GSK will pay [***] ([***]) separate

[***] to Isis for both the Base [***] Program and the Different Compound-Expanded [***] Program as set forth in [***] of [***]of [***] if and when such Development Milestone Event is achieved by a Compound from such [***] Program.

(g) **Milestone Payments for the [***] Program**. Section 1.6.2(d)(iv) and Section 1.6.2(e)(ii) above assume that the Development Milestone Events set forth in [***] of [***] will first be achieved by the Base [***] Program; provided, *however*, that irrespective

of whether achieved by a Compound in the Base [***] Program or the Expanded [***] Program, except as otherwise provided in Section 1.6.2(e)(ii), any Development Milestone Event achieved by a Compound being Developed under the [***] Program under Section 1.6.2(d) or Section 1.6.2(e) will trigger (i) the [***] ([***]) [***] for such Development Milestone Event set forth in [***] of [***] of [***] if such Compound is the first (1st) Compound under the [***] Program to achieve such Development Milestone Event; or (ii) the [***] ([***]) [***] for such Development Milestone Event set forth in [***] of [***]of [***] if such Compound is not the first (1st) Compound under the [***] Program to achieve such Development Milestone Event.

1.7. Collaboration Costs and Expenses.

1.7.1. Development Candidates.

(a) **PoC Cost Limit for Rare Disease Programs and [***] Program.** Subject to Section 1.7.2 below, Isis will be responsible for its costs and expenses in performing its obligations under Section 1.4 for each Collaboration Program and each Development Candidate; *except* with respect to the Rare Disease Programs and the [***] Program, Isis will only be responsible for paying the Phase 2 PoC Trial Costs of the Phase 2 PoC Trial for a Development Candidate up to a total of [***] ($[***]) (the "***PoC Cost Limit***"); *provided* that for any Phase 2 PoC Trial that involves [***] ([***]) or fewer patients, dosed at [***] ([***]) [***] or less per week, for [***] ([***]) [***] or less, Isis may only apply up to [***] ($[***]) of its Cost of Goods toward the PoC Cost Limit. If, for a Rare Disease Program or a [***] Program, the Phase 2 PoC Trial Costs for a Development Candidate are greater than the PoC Cost Limit, GSK [***] in order to complete the Phase 2 PoC Trial for such Development Candidate; *provided that* GSK will not have [***] Isis for the [***], including, without limitation, for the labor cost of Isis' employees who are clinical scientists, clinicians, and project managers. Isis' [***] to manufacture API [***] in accordance with APPENDIX 4.

(b) **IND-Supporting Toxicology Studies for Rare Disease Programs and [***] Program**. For clarity, for a Rare Disease Program or a [***] Program, Isis will conduct IND-Supporting Toxicology Studies at its cost for a duration of up to [***]([***]) months to support the dosing in up to a [***] ([***]) month Phase 2 PoC Trial; *provided*, *however*, if GSK requests that Isis conduct an IND-Supporting Toxicology Study that is longer than [***] ([***]) months, then GSK will pay Isis the costs of such longer study to the extent such costs exceed the cost of a [***] ([***]) month study, in accordance with a mutually agreed budget. Isis will

provide GSK with such a budget containing Isis' good-faith estimate of the cost of such longer IND-Supporting Toxicology Study. Isis' estimated budget of such costs shall be subject to GSK's approval; *provided*, *however*, that Isis has no obligation to conduct such longer IND-Supporting Toxicology Study unless and until Isis and GSK mutually agree on a budget.

(c) **Quarterly Invoice; Reimbursement True Up**. Isis will deliver to GSK an invoice for the portion of the budget attributable to the costs that exceed the PoC Cost Limit pursuant to Section 1.7.1(a) or the costs that exceed the costs of a [***] ([***]) month IND-Supporting Toxicology Study pursuant to Section 1.7.1(b) for the coming quarter on a quarterly basis no earlier than thirty (30) days prior to the beginning of such quarter, based on the approved budget for the applicable study, which GSK will pay within sixty (60) days after GSK's receipt. At the time Isis delivers its quarterly invoice to GSK, Isis shall also deliver to GSK a report summarizing the actual costs and expenses to conduct the applicable study in the previous quarter. GSK will reimburse Isis for such actual costs and expenses incurred by Isis in the previous quarter that is not covered by the advance payments made by GSK to Isis under Section 1.7.1(a) or Section 1.7.1(b) for such study for the previous quarter. GSK may use the balance of its advance payments to Isis for the previous quarter to offset its payment obligation for the coming quarter.

1.7.2. Special Funding Conditions Related to ID/Additional Programs.

(a) **In Vivo Efficacy Studies**. With respect to the ID/Additional Programs, Isis will conduct the pharmacology efficacy models specified in APPENDIX 2(B), including, but not limited to, the [***] model at its cost; *provided that* Isis will only be responsible for paying its external out-of-pocket costs (for clarity, excluding the cost of Isis' internal FTEs and Isis' costs to manufacture API) up to a total of $[***] and [***] such external costs incurred pursuant to a budget pre-approved by GSK to the extent such cost exceeds $[***] per ID/Additional Program. Isis will provide GSK with a budget containing Isis' good-faith estimate of such additional costs and the underlying activities. Isis' estimate of such costs shall be subject to GSK's approval; *provided*, *however*, that Isis has no obligation to conduct such activities unless and until Isis and GSK mutually agree on a budget.

(b) **IND-Supporting Toxicology Studies**. For clarity, for an ID/Additional Program, Isis will conduct IND-Supporting Toxicology Studies at its cost for a duration of up to [***] ([***]) months to support the dosing in up to a [***] ([***]) month Phase 2 PoC Trial; *provided*, *however*, if GSK requests that Isis conduct an IND-Supporting Toxicology Study that is longer than [***] ([***]) months, then GSK will pay Isis the costs of such longer study to the extent such costs exceed the cost of a [***] ([***]) month study, in accordance with a mutually agreed budget. Isis will provide GSK with such a budget containing Isis' good-faith estimate of the cost of such longer IND-Supporting Toxicology Study. Isis' estimated budget of such costs shall be subject to GSK's approval; *provided*, *however*, that Isis has no obligation to conduct such longer IND-Supporting Toxicology Study unless and until Isis and GSK mutually agree on a budget.

(c) **Clinical Studies**. In addition, with respect to the ID/Additional Programs, if the Early Development Plan includes studies that are in addition to or exceed the studies contemplated by APPENDIX 8(B), Isis will provide GSK with a budget containing Isis' good-faith estimate of the cost of such additional or expanded studies. Isis' estimate of such costs shall be subject to GSK's approval and GSK will be responsible for the costs set forth in the approved budget for conducting such additional or expanded studies; *provided*, *however*, that Isis has no obligation to conduct such activities unless and until Isis and GSK mutually agree on a budget and *provided*, *further*, that Isis will provide [***] and/or [***] for the studies designed in accordance with APPENDIX 8(B) [***].

(d) **Post PoC Tox Studies.** If the IDJSC agrees that post-PoC enabling activities such as long-term toxicity studies need to be initiated prior to exercise by GSK of an Option, GSK will propose the study design, timeline and drug product requirements to Isis. [***]; *provided that* Isis will provide up to [***] of API as required for such post-PoC enabling studies [***] per Collaboration Program.

(e) **Quarterly Invoice; Reimbursement True Up**. Isis will deliver to GSK an invoice for the portion of the budget attributable to the costs that exceed the [***] ($[***]) limit pursuant to Section 1.7.2(a), the costs that exceed the cost of a [***] ([***]) month study pursuant to Section 1.7.2(b) or the costs that exceed the cost of the IND-Supporting Toxicology Studies contemplated by APPENDIX 8(B) pursuant to Section 1.7.2(c), as the case may be, for the coming quarter on a quarterly basis no earlier than thirty (30) days prior to the beginning of such quarter, based on the approved budget for the applicable study, which GSK will pay within sixty (60) days after GSK's receipt. At the time Isis delivers its quarterly invoice to GSK pursuant to Section 1.7.2(a), 1.7.2(b) or 1.7.2(c) above, Isis shall also deliver to GSK a report summarizing the actual costs and expenses to conduct the applicable study in the previous quarter. GSK will reimburse Isis for such actual costs and expenses incurred by Isis in the previous quarter that is not covered by the advance payments made by GSK to Isis under Section 1.7.2(a), 1.7.2(b) or 1.7.2(c) for such study for the previous quarter. GSK may use the balance of its advance payments to Isis for the previous quarter to offset its payment obligation for the coming quarter.

1.7.3. **Back-Up Compounds.** [***] is responsible for [***] costs and expenses in performing its obligations under Sections 1.4.4(a) and 1.4.4(b) for any Back-Up Compound. If Isis is further Developing a Back-Up Compound beyond the Development Candidate status under Section 1.4.4(c), then [***] for all reasonable costs and expenses of advancing such Back-Up Compound beyond the stage of Development Candidate designation, subject to a budget approved in writing in advance by GSK.

1.7.4. **Follow-On Compounds.** [***] is responsible for [***] costs and expenses in performing its obligations to discover and Develop a Follow-On Compound to the Development Candidate stage pursuant to Section 1.4.5. Once a Follow-On Compound has reached the Development Candidate stage in accordance with this Agreement, [***] is [***] responsible, at [***] cost, for Developing and Commercializing such Follow-On Compound.

1.8. **End of Collaboration Term.** Upon the expiration of the Collaboration Term, (i) Isis will no longer have an obligation to perform any activities under Section 1.4.2; (ii) any Collaboration Programs that have not reached the [***] stage will no longer be Collaboration Programs and the applicable gene targets associated therewith will no longer be Collaboration Targets; (iii) Isis' obligations and GSK's rights under this Agreement with respect to such gene target and any ASOs targeting such gene target will then terminate, and Isis will be free to Develop and Commercialize on its own or with a Third Party such gene target and any Compounds targeting such gene target; and (iv) Isis will own any data generated under the Collaboration for such gene target and any Compounds targeting such gene target. For clarity, except to the extent explicitly set forth in the foregoing, the expiration of the Collaboration Term will not affect GSK's rights or Isis' obligations with respect to Collaboration Programs under this Agreement that have reached the [***] stage, including, but not limited to, Isis' obligation under Section 1.4.3 to Develop each such [***] under the remaining Collaboration Programs through the completion of the Phase 2 PoC Trial. Notwithstanding the foregoing, if Isis is not developing at least [***] ([***]) [***] under the applicable Collaboration Programs at the end of the Collaboration Term, (a) the Collaboration Term will be automatically extended for [***] ([***]) additional term of [***]([***]) [***] with respect to all Collaboration Programs that have reached the [***] stage, but have not generated a [***] by the end of the Collaboration Term, (b) Isis will continue its research and Development activities in accordance with Section 1.4.2 to generate [***] under such Collaboration Programs and (c) all rights and obligations of each Party with respect to such Collaboration Programs will remain the same during such extended [***] ([***]) [***] period. For clarity, (y) following the expiration of the Collaboration Term (including any such extension), Isis will continue to Develop each Development Candidate in accordance with each Early Development Plan through the completion of the Phase 2 PoC Trial, and (z) the automatic extension of the Collaboration Term set forth in this Section 1.8 cannot extend the Collaboration Term beyond the [***] ([***]) anniversary of the Effective Date.

1.9. **General Collaboration Matters**.

1.9.1. **Conduct of Collaboration.** Isis will conduct its work under the Collaboration in a good scientific manner, and in compliance with all applicable good laboratory practices, and all Applicable Laws, to use Commercially Reasonable Efforts to efficiently and expeditiously achieve the Objective of each Collaboration Program.

(a) Isis will, at its own expense and risk, maintain laboratories, offices, and all other facilities necessary to carry out its respective responsibilities under each Collaboration Program.

(b) Isis will maintain complete and accurate records of all work it conducts in the performance of each Collaboration Program and all results, data, inventions and developments made in the performance of each Collaboration Program. Such records will be in sufficient detail and in good scientific manner appropriate for patent and regulatory purposes.

1.9.2. **GSK Assistance in Collaboration.** In GSK's discretion, and as mutually agreed by GSK and Isis, GSK may, at GSK's cost and expense, assist Isis with certain of the

pharmacology studies for certain therapeutic areas included in the Collaboration, and, in the event GSK has access to animal models or other assays that Isis does not have in-house, GSK may perform portions of the Collaboration as mutually agreed therein. GSK will promptly provide Isis any data generated by GSK under this Section 1.9.2 for use in connection with the research, Development and Commercialization of Discontinued Products.

1.9.3. **Materials Transfer.** In order to facilitate the Collaboration, either Party may provide to the other Party certain materials for use by the other Party in furtherance of the Collaboration. All such materials will be used by the receiving Party in accordance with the terms and conditions of this Agreement solely for purposes of performing its rights and obligations under this Agreement, and the receiving Party will

not transfer such materials to any Third Party unless expressly contemplated by this Agreement or upon the written consent of the supplying Party.

1.9.4. **Additional Research/Opportunities.** In addition, under a separate, mutually agreed upon written research plan, the Parties may explore the opportunity for GSK and Isis to work together to further the technology, such as with formulation work, to allow [***], including exploring ways to [***]. GSK may present Isis with proposals regarding GSK's access to Isis' technology, outside of the Collaboration, which may include the formation of a joint venture with another party particularly as it relates to delivery technologies. Isis and GSK will evaluate and discuss such proposals in good faith, but will not be required to expand the scope of the Collaboration without executing a written agreement.

ARTICLE 2.
EXCLUSIVITY COVENANTS

2.1. **Isis' Exclusivity Covenants**.

2.1.1. **Isis' Exclusivity Covenants.** Except as set forth in Section 2.1.2 or in Section 9.3.2, prior to GSK's exercise of an Option, on a Collaboration Target-by-Collaboration Target basis, Isis agrees that it will not work independently of this Agreement for itself or any Affiliates or for or with any Third Party (including the grant of any license to any Third Party) with respect to discovery, research, development and/or commercialization activities of an ASO that is [***] a Collaboration Target for the period set forth below:

(a) **Collaboration Target.** Such exclusivity on a Collaboration Target will continue until the earlier of (i) the date such Collaboration Target is removed from the Collaboration in accordance with Section 1.5.2, 1.6.1 or 1.8; and (ii) the occurrence of an Option Deadline with respect to the applicable Collaboration Program and GSK does not exercise the Option for such Collaboration Program.

(b) **Licensed Program.** If GSK exercises its Option with respect to a Collaboration Program, then Isis' exclusivity obligations with respect to such Collaboration Program will continue with respect to the applicable Collaboration Target and any and all Development Candidates, Licensed Compounds and Licensed Products under such Collaboration Program for so long as the exclusive license under Section 4.1.1 for the applicable Collaboration Program remains in effect.

2.1.2. **Limitations and Exceptions to Isis' Exclusivity Covenants.** Notwithstanding anything to the contrary in this Agreement, Isis' practice of the following will not violate Section 2.1.1:

(a) Any activities pursuant to the Prior Agreements;

(b) Permitted Licenses;

(c) Isis (for itself and not for a Third Party) will be permitted to discover, research and develop with respect to the Collaboration Target within such Collaboration Program (an "***Isis Follow-On Product***") if (1) (i) GSK does not ask Isis to identify a Follow-On Compound for a Collaboration Program under Section 1.4.5 prior to the applicable Development Candidate successfully completing its first (1st) [***], or (ii) Isis identifies a Follow-On Compound for a Collaboration Program under Section 1.4.5, but thereafter GSK does not use Commercially Reasonable Efforts to continue to Develop and Commercialize such Follow-On Compound (on its own or with Isis); and (2) all [***]; *provided*, *however*, that (y) Isis will not have the right to develop or commercialize any Licensed Product being Developed or Commercialized by GSK under this Agreement, and (z) Isis hereby provides GSK with a [***]; and

(d) After any exercise by GSK of its Option for the [***] Programs, if GSK is Developing or Commercializing the [***] Program for [***] ("***[***] Program***"), and is not Developing or Commercializing the [***] Program for [***] ("***[***] Program***"), Isis may Develop and Commercialize ASOs under a [***] Program in accordance with the following conditions:

(i) Isis will have no access to, nor will GSK be obligated to grant Isis, a license to any of the Isis Product-Specific Patents assigned by Isis to GSK under this Agreement related to the [***] Program;

(ii) Isis' ASO for [***] will not have [***] to the Licensed Compound or Licensed Product within GSK's [***] Program for [***];

(iii) Isis will not grant a Third Party a license to Isis' [***] Program until such program reaches the [***] stage of Development, at which time GSK will have a [***] with respect to such [***] Program [***], *mutatis mutandis*;

(iv) If Isis and GSK do not consummate a license agreement for the [***] Program during GSK's [***], then during (i) the period in which there is an issued claim within a patent Controlled by GSK in a Major Country Covering the composition of matter or approved method of use of the Licensed Compound or Licensed Product in the [***] Program or (ii) the data exclusivity period conferred by the applicable Regulatory Authority in such country with respect to such Licensed Product (such as in the case of an orphan drug), Isis will not, and will not allow its Third Party partner, to do any of the following:

[***].

(v) Isis will include GSK as an intended third party beneficiary in its agreement with a Third-Party partner for the [***] Program, solely to allow GSK to enforce the obligations and restrictions set forth in this Section 2.1.2(d) directly against such Third Party partner; and

(vi) As long as there is (i) an issued claim within a patent Controlled by GSK in a Major Country Covering the composition of matter or approved method of use of the Licensed Compound or Licensed Product in the [***] Program or (ii) a data exclusivity period conferred by the applicable Regulatory Authority in such country with respect to such Licensed Product (such as in the case of an orphan drug), Isis will pay GSK royalties [***] on Net Sales by Isis, its Affiliates or its Third-Party partner of such ASO within the [***] Program arising from prescriptions written by [***] or [***] for any [***] Indications in any Major Country (as determined by IMS data).

(e) After any exercise by GSK of its Option for the [***] Programs, if such [***] Programs include both [***] and [***] and GSK is not Developing or Commercializing a Compound or Licensed Product for [***], Isis may Develop and Commercialize an ASO for [***], *provided that* Isis satisfies the conditions set forth in Section 2.1.2(d)(i) through Section 2.1.2(d)(vi) above.

For the avoidance of doubt, so long as GSK is Developing or Commercializing a Licensed Compound or Licensed Product for [***] via [***] in accordance with this Agreement, Isis will not have the right to Develop or Commercialize any ASO for [***].

2.1.3. Except as otherwise expressly provided in this Agreement, Isis will not enter into any research or development collaborations with a Third Party that would or be reasonably likely to diminish Isis' ability to perform its obligations under this Agreement in any material respect.

2.2. GSK's Exclusivity Covenants.

2.2.1. GSK's Exclusivity Covenants. Except as set forth in Section 2.2.2 or in Section 9.3.1, on a Collaboration Target-by-Collaboration Target basis and solely with respect to a Collaboration Target that Isis has generated a Development Candidate, GSK agrees that it will not work independently of this Agreement for itself or any Affiliates or for or with any Third Party in researching or Developing a nucleic acid—based approach [***] with respect to a Collaboration Target that has generated a Development Candidate until the earlier of (i) the date such Collaboration Target is removed from the Collaboration in accordance with Section 1.5.2, 1.6.1 or 1.8; and (ii) the date GSK elects to exercise or declines to exercise its Option with respect to the Collaboration Program relating to such Collaboration Target.

2.2.2. Limitations and Exceptions to GSK's Exclusivity Covenants. Notwithstanding anything to the contrary in this Agreement, GSK's practice of the following will not violate Section 2.2.1:

(a) Modalities other than Antisense;

(b) [***] the practice of which is [***]; and

(c) GSK continuing its (i) internal research and development efforts and (ii) collaborative work with a Third Party with respect to any gene target unless and until such gene target is a Collaboration Target with respect to which Isis has generated a Development Candidate. If GSK (by itself or with a Third Party) is researching or developing a nucleic acid-based therapeutic [***] against a Collaboration Target outside of the Collaboration, GSK will provide Isis with written notice thereof on the Effective Date, or at the time such Collaboration Target is proposed for inclusion in this Agreement, as applicable, which notice will only state that GSK is researching or developing a nucleic acid-based therapeutic [***] against a Collaboration Target outside of the Collaboration without disclosing any other information.

2.3. Effect of Exclusivity on Future Indications. Each Collaboration Program is focused on delineated gene targets that are known to play a role in certain therapeutic areas. Nevertheless, GSK's license to any drugs arising therefrom will not be limited to a particular therapeutic area or Indication. Isis is subject to exclusivity obligations under Section 2.1 of this Agreement with respect to Collaboration Targets; *however*, GSK acknowledges and agrees that, except as prohibited under Section 2.1 above, Isis (on its own or with a Third Party) may continue to discover, research, develop and commercialize products for any Indication, including Indications in the same therapeutic areas as a Collaboration Program.

ARTICLE 3.
EXCLUSIVE OPTION; MANUFACTURING

3.1. Option. On a Collaboration Program-by-Collaboration Program basis, on or before 5:00 p.m. (Eastern time) on the [***] ([***]) day (each, an "***Option Deadline***") following GSK's receipt of (i) written notice from Isis regarding the completion of the first Phase 2 PoC Trial for the applicable Development Candidate, and (ii) the applicable Phase 2 PoC Data Package (such notice and package, a "***PoC Trial Completion Notice***"), GSK will have the exclusive option to obtain from Isis the license set forth in Section 4.1.1 below. GSK will notify Isis whether GSK is exercising its option to license the Collaboration Program by notifying Isis in writing on or before the applicable Option Deadline.

3.1.1. If GSK does not notify Isis before the applicable Option Deadline of GSK's determination to license a Collaboration Program, then GSK's option under Section 3.1 with respect to such Collaboration Program will expire and, subject to Section 5.10, Isis will be free to develop and commercialize any Compounds that were included in such Collaboration Program on its own or with a Third Party. In such a case, except as specified in Section 5.10, GSK will have no further rights to such Collaboration Program (including all Compounds included therein) and the gene target to which such Development Candidate is

directed will no longer be a Collaboration Target. Following any expiration of an Option under this Section 3.1.1, GSK will promptly transfer to Isis all data, results and information related to the testing and studies in the Collaboration Program in the possession of GSK and

its contractors to the extent such data, results and information were generated by or on behalf of GSK under this Agreement.

3.1.2. If GSK notifies Isis in writing before the applicable Option Deadline of GSK's determination to exercise an Option for a Collaboration Program, Isis will grant to GSK the license set forth in Section 4.1.1 for such Collaboration Program.

3.1.3. **Early Exercise of an Option.** For the avoidance of doubt, notwithstanding anything to the contrary in this Agreement, GSK will have the right to exercise any Option prior to GSK's receipt of a PoC Trial Completion Notice by notifying Isis in writing of GSK's good-faith intent to exercise its Option for the applicable Collaboration Program. In such event, Isis will promptly provide GSK the Phase 2 PoC Data Package, to the extent available, for the applicable Collaboration Program. If, before the applicable Option Deadline, GSK then notifies Isis that it is exercising its Option early under this Section 3.1.3, Isis will grant to GSK the license under Section 4.1.1 for such Collaboration Program on the terms and conditions of this Agreement (including, without limitation, the terms and conditions of ARTICLE 5). In the event that GSK does not exercise such Option early under this Section 3.1.3, such Collaboration Program will continue to be subject to exercise of an Option until the applicable Option Deadline under Section 3.1.

3.2. **HSR Compliance**.

3.2.1. If either Party reasonably determines it is required for the exercise of any Option, each Party will use commercially reasonable efforts to satisfy any applicable requirements under HSR, and the regulations promulgated thereunder, including by making an initial HSR filing no later than five (5) days after GSK's delivery of written notice of its exercise of an Option, or upon such other timing as mutually agreed by the Parties.

3.2.2. Each Party will cooperate with the other Party in the prompt preparation, execution and filing of all documents that are required or permitted to be filed pursuant to HSR, and to notify the other Party upon receipt of any formal or informal requests for information from any antitrust agency in connection with any filings under HSR. Each Party will bear its own costs and expenses with respect to performing its obligations under this Section 3.2 and complying with HSR.

3.2.3. No exercise of an Option will be effective until the date (the "***Option Exercise Effective Date***") when either (a) the requirements described in this Section 3.2 have been satisfied and all applicable waiting periods (including any extensions thereof) under HSR have expired or been terminated, or (b) GSK delivers to Isis a legal opinion addressed to Isis from a nationally recognized law firm that no HSR filings are required hereunder with respect to the exercise of such Option.

3.3. **Manufacturing**.

3.3.1. Isis will Manufacture and supply API for each Collaboration Program through [***]. Such API will be Manufactured with systems, processes and procedures consistent with cGMP practices. The Parties may discuss, without obligation, the continued Manufacture and supply of API for Development Candidates after [***].

3.3.2. Following the exercise of any Option hereunder, GSK will notify Isis in writing of GSK's good faith intention to use a Third Party to Manufacture clinical supplies of API for any Licensed Compound(s) or Licensed Products. Isis will have thirty (30) days from the receipt of such notice to notify GSK in writing whether Isis desires to negotiate with GSK regarding the Manufacture of the API for such Licensed Compound(s). If Isis fails to respond to GSK's notice within such thirty (30) day period, or if Isis declines in writing to exercise its right of first negotiation, then GSK will be free to use a Third Party to Manufacture and supply the API for such Licensed Compound(s) and Isis shall promptly transfer its Licensed Know-How to such Third Party pursuant to Section 4.2.1 solely for use by such Third Party to Manufacture API for such Licensed Compound(s) for GSK. If Isis wishes to Manufacture the API for such Licensed Compound(s), the Parties will negotiate in good faith the terms of a manufacturing agreement regarding clinical supplies of such API. If, despite good-faith negotiations, GSK and Isis do not reach an agreement within ninety (90) days from Isis' exercise of its right of first negotiation, then GSK will be free to use a Third Party to Manufacture and supply the API for such Licensed Compound(s) on terms, which, when taken as a whole, are not more favorable than the terms last offered to Isis by GSK.

ARTICLE 4.
LICENSE GRANTS TO GSK; DEVELOPMENT AND DILIGENCE; FOLLOW-ON COMPOUNDS

4.1. **License Grants to GSK**.

4.1.1. **Development and Commercialization License**. On a Collaboration Program-by-Collaboration Program basis, subject to the terms and conditions of this Agreement, Isis hereby grants to GSK a worldwide, exclusive, royalty-bearing, sublicensable (in accordance with Section 4.1.2 below) license under the Licensed IP to Manufacture, Develop, and Commercialize Licensed Compounds and Licensed Products.

Notwithstanding the foregoing, (A) the licenses granted by Isis under this Section 4.1.1 are only effective upon (i) compliance with Section 3.2 above, and (ii) GSK's exercise of any Option or by operation of the applicable termination provisions of Section 9.3.1 or Section 12.4 wherein the effect of such provisions is the grant of an exclusive license to GSK under this Section 4.1.1; and (B) with respect to Isis' [***] Programs, the license granted by Isis under this Section 4.1.1 will be limited to the [***] Field, subject to Section 2.1.2(d).

4.1.2. **Sublicense Rights**.

(a) Subject to the terms and conditions of this Agreement and at no additional costs to GSK, GSK will have the right to grant to its Affiliates and/or Third Parties sublicenses under the licenses granted under Section 4.1.1 above, in each case

solely to further the Development and/or Commercialization of a Licensed Compound and/or Licensed Product; *provided that* each such sublicense will (i) be subject to, and consistent with, the applicable terms and conditions of this Agreement; and (ii) name Isis as an intended third party beneficiary with the right to directly enforce the applicable terms and conditions of this Agreement against such Affiliate or Sublicensee. GSK will provide Isis with a redacted copy of any sublicense granted pursuant to this Section 4.1.2 within thirty (30) days after the execution thereof; *provided* such redacted copy will at a minimum provide the information necessary for Isis to determine GSK's and such Sublicensee's compliance with this Agreement.

(b) **Effect of Termination on Sublicenses**. If this Agreement terminates for any reason, any Sublicensee will, from the effective date of such termination, automatically become a direct licensee of Isis with respect to the rights originally sublicensed to the Sublicensee by GSK, and GSK agrees that it will confirm the foregoing in writing at the request and for the benefit of Isis and/or the Sublicensee; *provided*, *however*, that (i) such Sublicensee is not in breach of its sublicense agreement, (ii) such Sublicensee agrees to comply with all of the terms of this Agreement to the extent applicable from the rights originally sublicensed to it by GSK, and (iii) such Sublicensee agrees to pay directly to Isis such Sublicensee's payments under this Agreement to the extent applicable to the rights sublicensed to it by GSK.

4.1.3. **No Implied Licenses**. All rights in and to Licensed IP not expressly licensed to GSK hereunder or pursuant to the operation of the relevant applicable express provisions of this Agreement, and any other Patent Rights or Know-How of Isis or its Affiliates, are hereby retained by Isis or its Affiliates. All rights in and to GSK Technology not expressly licensed to Isis under Section 10.1 or pursuant to the operation of the relevant applicable express provisions of this Agreement, and any other Patent Rights or Know-How of GSK or its Affiliates, are hereby retained by GSK or its Affiliates. Except as expressly provided in this Agreement, no Party will be deemed by estoppel or implication to have granted the other Party any license or other right with respect to any intellectual property of such Party.

4.1.4. **License Conditions; Limitations**. Subject to Section 5.11, any license granted under Section 4.1.1 and the sublicense rights under Section 4.1.2 are subject to and limited by (i) any applicable Third Party Obligations, and (ii) the Prior Agreements, in each case to the extent provisions of such obligations or agreements are specifically disclosed to GSK in writing prior to GSK's exercise of the applicable Option. Isis will disclose to GSK the applicable Third Party Obligations each time (x) Isis provides GSK with a Development Candidate Package under Section 1.4.2(c); and (y) Isis provides GSK with a Phase 2 PoC Data Package under Section 3.1.

4.1.5. **Trademarks for Licensed Products**. If GSK has exercised its Option with respect to a Collaboration Program hereunder, to the extent that (i) Isis owns any trademark(s) which Isis used prior to the exercise of the Option, (ii) such trademarks are specific to any Licensed Compound developed under such Collaboration Program, and (iii) GSK

reasonably believes such trademark(s) would be reasonably necessary or useful for the marketing and sale of such Licensed Compound or related Licensed Product, then Isis will, upon GSK's request and at GSK's sole cost and expense relating to such assignment, assign its rights and title to such trademark(s) to GSK reasonably in advance of the First Commercial Sale of such Licensed Products (but in no event prior to NDA Filing for such Licensed Product). Other than the trademarks described above which are owned by Isis prior to the exercise of an Option by GSK, GSK will be solely responsible for developing, selecting, searching, registering and maintaining, and will be the exclusive owner of, all trademarks, trade dress, logos, slogans, designs, copyrights and domain names used on and/or in connection with any of the Licensed Compounds and Licensed Products resulting from a Collaboration Program.

4.1.6. **New Licensed Know-How**. During the Agreement Term, at no additional cost or expense to GSK, Isis will provide all Licensed Know-How that has not previously been provided hereunder for use solely in accordance with the licenses granted under Section 4.1.1. Isis will provide such Licensed Know-How promptly upon such Licensed Know-How coming under the control of Isis.

4.1.7. **Subcontracting.** Each Party will have the right to engage Third-Party subcontractors to perform certain of its obligations under this Agreement; *provided that* Isis will not have the right to subcontract, in whole or in part, any activities to be performed by Isis under this Agreement if doing so would be inconsistent with Isis' normal business practices for its own programs as of the Effective Date. Any subcontractor to be engaged by a Party to perform a Party's obligations set forth in the Agreement will meet the qualifications typically required by such Party for the performance of work similar in scope and complexity to the subcontracted activity. Notwithstanding the preceding, any Party engaging a subcontractor hereunder (including, without limitation, for the performance of clinical trials) will remain responsible and obligated for such activities and will in all cases retain or obtain exclusive Control (i.e., either ownership or an exclusive, sublicenseable license or an option to obtain such a license) of any and all intellectual property created by (or used with the relevant Party's permission by) such subcontractor directly related to such subcontracted activity, at the sole cost and expense of the Party engaging such subcontractor, and any such costs and expenses will be included in Isis Supported Pass-Through Costs or GSK Supported Pass-Through Costs, as the case may be. To the extent that such exclusive Control of rights cannot be obtained by Isis with respect to any intellectual property from any such subcontractor of Isis, prior to entering into any such arrangement with any such subcontractor, Isis will bring such matter to GSK in writing in a timely fashion in order to seek the prior written consent from GSK to enter into such an arrangement, such consent not to be unreasonably withheld. For clarity, this Section 4.1.7 will not apply to restrict or otherwise limit the rights of GSK to use a subcontractor after the exercise of its Option or the acquisition of exclusive rights to the Collaboration Compounds of a Collaboration Program pursuant to the express provisions of Section 9.3.1 and Section 12.4 for the relevant Collaboration Program.

4.2. **Technology Transfer after Exercise by GSK of an Option**.

4.2.1. **Generally**. Isis will promptly, but no later than [***] ([***]) [***] after GSK exercises its Option for a Collaboration Program hereunder, deliver to GSK and/or GSK's Third-Party designee solely for use by such Third Party to Manufacture API for such Licensed Compound(s) for GSK, if Isis does not elect to Manufacture the API for GSK under Section 3.3.2, [***], all Licensed Know-How in Isis' Control relating to the Compounds included in such Collaboration Program, including, but not limited to, (a) information regarding the bulk

drug substance and methods of manufacturing the same, including bulk and final product manufacturing processes, manufacturing data, batch records, vendor information and validation documentation, which is necessary or useful for the exercise by GSK of the Manufacturing rights granted under Section 4.1.1; (b) pre-clinical and clinical data and results (including pharmacology, toxicology, emulation and stability studies), adverse event data, protocol results and analytical methodologies; (c) copies of patent applications and patents included within Isis Product-Specific Patents and other relevant patent information; and (d) regulatory filings (including all relevant INDs and Approvals), regulatory documentation, regulatory correspondence, and applicable reference standards relating to the applicable Licensed Compounds to the extent permitted under applicable law, *provided*, *that*, at GSK's reasonable discretion if no such transfer is reasonably practical, then Isis will grant to GSK a right of reference to such regulatory filings; and (e) pursuant to a mutually agreed supply agreement, bulk drug substance or other materials, including drug substance, drug product and intermediate stocks, reference standards and analytical specification and testing methods used to Manufacture the applicable Licensed Compounds, as well as any then-existing supplies of such materials, which are deemed suitable by GSK, of such Licensed Compounds, including Back-Up Compounds and other Licensed Compounds under such Collaboration Program. Further, Isis shall, in good faith and [***], provide up to [***] ([***]) hours of support to GSK, including, but not limited to, its internal resource, to enable GSK to successfully manufacture at least one (1) post-technology transfer demonstration batch of Licensed Product. If GSK desires to receive additional support from Isis beyond such initial [***] ([***]) hours, GSK will pay Isis to provide such assistance at the FTE Rate. All information should be supplied to GSK in electronic format to the extent possible. Without limiting the foregoing, Isis will use Commercially Reasonable Efforts to perform the transfer of such information and materials to GSK in an orderly manner, without undue interruption of Isis' business operations and GSK's Development of Licensed Compounds and related Licensed Products hereunder. Upon delivery of such information and materials to GSK, GSK will use Commercially Reasonable Efforts to promptly implement such information and materials into its Development and Commercialization activities with respect to such Licensed Compounds and related Licensed Products hereunder. For the avoidance of doubt, the obligation on Isis to deliver to GSK all Licensed Know-How and other information in accordance with this Section 4.2.1 will include the use of Commercially Reasonable Efforts to procure any Licensed Know-How in the possession of any Third Party subcontractor engaged by Isis as a subcontractor in the performance of the Collaboration Program.

4.2.2. **Additional Services**. In the event that GSK reasonably requests Isis to provide GSK with any materials or services beyond those set forth in Section 4.2.1, such materials and/or services may be scheduled and provided by Isis to GSK on such terms and conditions as may be mutually agreed between the Parties at the time of any such request, if the Parties mutually desire to engage in the transfer or provision of such additional materials or services.

4.3. **GSK Diligence.** As soon as practicable after the exercise by GSK of an Option for a Collaboration Program, GSK will use Commercially Reasonable Efforts to promptly commence and pursue a program of ongoing Development and Commercialization for the Licensed Compound and related Licensed Product under such Collaboration Program, in accordance with GSK's diligence obligations set forth below. GSK will be solely responsible for all Development and Commercialization activities, and for all costs and expenses associated therewith, with respect to the Development, Manufacture and Commercialization of the Licensed Compound and related Licensed Product of a Collaboration Program, following the exercise of its Option for such Collaboration Program, and will exercise Commercially Reasonable Efforts in Developing and Commercializing such Licensed Product for each Collaboration Program for which GSK exercises the Option.

4.3.1. **Specific GSK Responsibilities.** Without limiting any of the foregoing, following the exercise of an Option for a Collaboration Program hereunder, GSK will use Commercially Reasonable Efforts to:

(a) conduct all Pre-Clinical Studies and Clinical Studies on the Licensed Compound and related Licensed Product as deemed necessary or desirable by GSK or any applicable Regulatory Authority, but at a minimum consistent with the level and type of activities GSK would reasonably conduct for its other compounds or products of similar market potential at similar stages in development or product life;

(b) conduct additional formulation development of the Licensed Compound and related Licensed Product as and if deemed necessary or appropriate by GSK;

(c) provide to Isis reasonable progress updates and product plans in accordance with Section 4.3.2 and Section 4.3.3 below on the status of GSK's Development and Commercialization efforts with respect to the Licensed Compounds and related Licensed Products;

(d) prepare and file all regulatory filings for the Licensed Compound or related Licensed Product, including all INDs, NDAs and other filings;

(e) except as provided in Section 3.3.2, Manufacture or have Manufactured (including process development and scale up) bulk drug substance or drug product material with respect to the Licensed Compound and related Licensed Product for ongoing Development and Commercialization requirements, consistent with GSK's internal practices and all Applicable Laws;

(f) own and maintain INDs, NDAs, Approvals and other regulatory filings and approvals, and brands and trademarks for any resulting Licensed Product;

(g) maintain a safety database with respect to the Licensed Compound and related Licensed Product Developed and Commercialized by GSK, and report all adverse drug reaction experiences related to such Licensed Compound and Licensed

Product in connection with the activities of GSK under this Agreement to the appropriate Regulatory Authorities in which the Licensed Compound and related Licensed Product are being Developed and Commercialized, in accordance with Applicable Laws

of the relevant countries and Regulatory Authorities and in accordance with GSK's internal policies and, without limiting Section 4.4, GSK will provide Isis with such safety-related information as required under Section 4.4; and

(h) conduct, at GSK's sole expense, Commercialization activities in connection with the marketing, promotion, and sale of such Licensed Product.

4.3.2. **Development Status Reports by GSK.** After GSK exercises its Option for a Collaboration Program hereunder, GSK agrees to keep Isis informed with respect to activities and progress with the Development of the Licensed Compound and related Licensed Product, and agrees to provide to Isis every six (6) months a written summary of such activities and progress. Each such report will contain the same summary information of all key strategic decisions and management approvals regarding a Licensed Compound and related Licensed Product as presented in the report provided to the internal GSK committee primarily responsible for overseeing the Development of the particular Licensed Compound and related Licensed Product; *provided* that GSK may redact all unrelated information and all information belonging to a Third Party that is the subject of an agreement between GSK and such Third Party that prevents GSK from disclosing such information to Isis.

4.3.3. **Product Development Plans; Integrated Product Plans.** For each Licensed Product Developed by GSK under this Agreement, GSK will prepare a Development plan outlining key aspects of the Development of such Licensed Product through Approval. GSK will prepare each Development plan at the same time and containing information consistent with GSK's Development plans for its similar products at similar stages of development (each a "***Product Development Plan***"). In addition, GSK will prepare a global integrated Licensed Product plan outlining the key aspects of market launch and Commercialization (the "***Integrated Product Plan***" or "***IPP***"). GSK will prepare each IPP at the same time and containing information and target markets as customarily contained in GSK's Commercialization plans for its similar products at similar stages of development. Once GSK has prepared such plans, GSK will update each Product Development Plan and IPP consistent with GSK's standard practice and provide such update to Isis annually. GSK and Isis will meet on a yearly basis to discuss the draft of each Product Development Plan and IPP and GSK will consider, in its sole discretion, any proposals and comments made by Isis for incorporation in the final Product Development Plan or IPP (as the case may be). Notwithstanding the foregoing, following the closing of any Change of Control with respect to Isis, this Section 4.3.3 will no longer apply to GSK.

4.3.4. **Class Generic Claims.** To the extent GSK intends to make any claims in a Licensed Product label that are class generic to ASOs, GSK will provide such claims to Isis in advance and will [***] any proposals and comments made by Isis.

4.4. **Safety Database**.

4.4.1. Isis maintains a database that includes information regarding the tolerability of its drug compounds, individually and as a class, including information discovered during pre-clinical and clinical development (the "***Isis Database***"). In an effort to maximize understanding of the safety profile and pharmacokinetics of Isis compounds, after GSK exercises its Option for a Collaboration Program hereunder, GSK will cooperate in connection with populating the Isis Database. To the extent collected by GSK and in the form in which GSK uses/stores such information for its own purposes, GSK will provide Isis with information concerning toxicology, pharmacokinetics, safety pharmacology study(ies), serious adverse events and other safety information related to each Licensed Compound and Licensed Product as soon as practicable following the date such information is available to GSK (but not later than thirty (30) days after GSK's receipt of such information). In connection with any reported serious adverse event, GSK will provide Isis all serious adverse event reports, including initial, interim, follow-up, amended, and final reports. In addition, with respect to each Licensed Compound and Licensed Product, GSK will provide Isis with copies of annual safety updates filed with each IND and the safety sections of any final Clinical Study reports within thirty (30) days following the date such information is filed or is available to GSK, as applicable. Furthermore, GSK will promptly provide Isis with any supporting data and answer any follow-up questions reasonably requested by Isis. All such information disclosed by GSK to Isis will be GSK Confidential Information; *provided*, *however*, that Isis may disclose any such GSK Confidential Information to (a) Isis' other partners pursuant to Section 4.4.2 below if such information is regarding class generic properties of ASOs, and/or (b) any Third Party, in each case, so long as Isis does not disclose the identity of the Licensed Compound, Licensed Product, or GSK. GSK will deliver all such information to Isis for the Isis Database to Isis Pharmaceuticals, Inc., 1896 Rutherford Road, Carlsbad, California 92008, Attention: Chief Medical Officer (or to such other address/contact designated in writing by Isis).

4.4.2. From time to time, Isis utilizes the information in the Isis Database to conduct analyses to keep Isis and its partners informed regarding class generic properties of ASOs, including with respect to safety. As such, if and when Isis identifies safety or other related issues that may be relevant to a Licensed Compound and Licensed Product (including any potential class-related toxicity), Isis will promptly inform GSK of such issues and, if requested, provide the data supporting Isis' conclusions.

ARTICLE 5.
FINANCIAL PROVISIONS

5.1. **Overview.** The specific amount of each payment GSK is required to make under this ARTICLE 5 will depend on whether the Collaboration Program is a Rare Disease Program, a [***] Program or an ID/Additional Program; and additionally with respect to the [***] Program, whether the payment is triggered by the first Indication, second Indication, and/or the Different Compound-Expanded [***] Program. As such, the provisions in this ARTICLE 5 contain tables that specify the amount of each payment applicable to each type of Collaboration Program, and with respect to [***] Programs and ID/Additional Programs, whether such milestone is achieved in the first or second Indication. For purposes of clarity, each [***] that GSK elects to continue under Section

1.6.1 will be counted as a separate and distinct Collaboration Program under this Agreement, such that by way of example and not limitation, if GSK exercised its Option for [***], GSK would pay Isis [***] ([***]) separate $[***] Option exercise fees under Column 1 of Table 1 in Section 5.4, and Isis would be eligible to receive [***] ([***]) [***] of milestone payments (totaling $[***] for each Collaboration Program, and $[***] in the

aggregate) under Column 1 of Table 2 in Section 5.5. For purposes of clarity, the Different Compound-Expanded [***] Program will be counted as a separate and distinct Collaboration Program from the Base [***] Program under Section 5.4 and Section 5.5, such that by way of example and not limitation, GSK would pay Isis [***] ([***]) separate $[***] Option exercise fees under Column 2 of Table 1 in Section 5.4, Isis would be eligible to receive [***] ([***]) [***] of milestone payments for the first Indication (totaling $[***] for each Collaboration Program, and $[***] in the aggregate) under Column 2 of Table 2 in Section 5.5 and [***]([***]) [***] of milestone payments for the second Indication (totaling $[***] for each Collaboration Program, and $[***] in the aggregate) under Column 3 of Table 2 in Section 5.5. The Base [***] Program is a part of the Same Compound-Expanded [***] Program, and GSK's exercise of its option to expand the [***] Program to include the Same Compound-Expanded [***] Program pursuant to Section 1.6.2(d) will not entitle Isis to receive additional sets of payments under Section 5.4 and Section 5.5; *provided, however*, that if GSK exercises such expansion option after the [***] stage under Section 1.6.2(e), GSK will pay the first Indication milestone payments under Column 2 of Table 2 in Section 5.5 for both the Base [***] Field and the Expanded [***] Field for Development Milestone Events after [***] but through and including the first [***] (totaling $[***] for the Base [***] Program and $[***] for the Same Compound-Expanded [***] Program, and $[***] in the aggregate) and will thereafter resume milestone payments in accordance with Table 2 of Section 5.5 for first and second Indications, as applicable. The purpose of this Section 5.1 is to provide examples of certain actual payments Isis is eligible to receive hereunder and a high-level overview of the financial terms under this Agreement, and therefore this Section 5.1 is qualified in its entirety by the more detailed financial provisions in the remainder of this ARTICLE 5.

5.2. **Up-Front Payment**. In partial consideration for GSK's Options hereunder, within five (5) Business Days following the Effective Date and receipt of an invoice by GSK, GSK will pay Isis a technology access fee equal to $35,000,000.

5.3. **Other Payments**.

5.3.1. If GSK elects to add a sixth (6^{th}) Collaboration Program to this Agreement under Section 1.4.1, then GSK will pay Isis the $[***] payment specified in Section 1.4.1.

5.3.2. If GSK elects to pursue [***] ([***]) [***] under Section 1.6.1, then GSK will pay Isis a $[***] payment as further specified in Section 1.6.1.

5.3.3. If GSK elects to expand the Base [***] Program to include the Same Compound-Expanded [***] Program pursuant to Section 1.6.2(d), then GSK will pay Isis the milestone payments in accordance with Section 1.6.2(d). If GSK elects to pursue the Same Compound-Expanded [***] Program pursuant to Section 1.6.2(e), then GSK will pay Isis the $[***] payment specified in Section 1.6.2(e). If GSK elects to pursue the Different Compound-Expanded [***] Program pursuant to Section 1.6.2(f), then GSK will pay Isis the $[***] payment specified in Section 1.6.2(f).

5.4. **Option Exercise Fees**. On an Option-by-Option basis, upon the exercise by GSK of an Option for a given Collaboration Program in accordance with Section 3.1, GSK will pay to Isis an Option exercise fee in accordance with Table 1 below (as determined by the type of Collaboration Program for which GSK so exercised its Option) within [***] ([***]) days of receipt by GSK of an invoice sent from Isis on or after the Option exercise becomes effective pursuant to Section 3.2. For purposes of clarification, except as set forth in Section 1.6.2(f) for any Option exercised by GSK for a Different Compound-Expanded [***] Program, once GSK has paid the Option exercise fee under this Section 5.4 in connection with the exercise of an Option, then GSK will not be required to pay a second exercise fee for any Follow-On Compound, Back-Up Compound or other Licensed Compound under the same Collaboration Program Developed and Commercialized by GSK.

Table 1

	Column 1 Each Rare Disease Program	Column 2 Each [***] Program	Column 3 Each ID/Additional Program
Option Exercise Fee	$ [***]	$ [***]	$ [***]

5.5. **Milestone Payments for Achievement of Development Milestone Events for Rare Disease Programs or [***] Programs**.

5.5.1. **Milestone Payments for First Achievement of Development Milestone Event**. On a Collaboration Program-by-Collaboration Program basis in either a Rare Disease Program or a [***] Program, GSK will pay to Isis the applicable one-time milestone payments as set forth in Table 2 below (as determined by the type of Collaboration Program to achieve such event, and with respect to the [***] Programs, whether the first Indication or second Indication achieved such event, subject to Section 1.6.2) after a Licensed Product that is part of such Collaboration Program first achieves the events (each, a "***Development Milestone Event***") listed in Table 2 by or on behalf of GSK or its Affiliates or Sublicensees.

Table 2

Development Milestone Events for a Licensed Product	Column 1 Each Rare Disease Program	Column 2 Each [***] Program (1st Indication)	Column 3 Each [***] Program (2nd Indication)
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]

[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]
Total Development Milestone Payments per Collaboration Program	**[***]**	**[***]**	**[***]**

5.5.2. **Development Milestone Payments for Follow-On Compounds**. For each Collaboration Program that is either a Rare Disease Program or a [***] Program for which GSK has requested a Follow-On Compound under Section 1.4.5, (i) upon the designation of a Follow-On Compound as a Development Candidate, GSK will pay to Isis a milestone payment equal to [***] ($[***]), and (ii) when such Follow-On Compound first achieves a listed Development Milestone Event, by or on behalf of GSK or its Affiliates or Sublicensees, [***] percent ([***]%) of the milestone payments for such Development Milestone Event set forth in Table 2 above if such Follow-On Compound is the first Licensed Product under the applicable Option to achieve such Development Milestone Event, or in amounts that are [***] percent ([***]%) of the applicable milestone payments for such Development Milestone Event set forth in Table 2 above if such Follow-On Compound is not the first Licensed Product under the applicable Option to achieve such Development Milestone Event.

5.6. **Milestone Payments for Achievement of Development and Regulatory Milestone Events by ID/Additional Program**.

5.6.1. **Milestone Payments for First Achievement of Milestone Event**. On a Collaboration Program-by-Collaboration Program basis and with respect to the ID/Additional Program, GSK will pay to Isis the applicable one-time milestone payments as set forth in Table 3 below (as determined by whether the first or second Indication achieves such event) after a Licensed Product that is part of such Collaboration Program first achieves the Development Milestone Event listed in Table 3, by or on behalf of GSK or its Affiliates or Sublicensees. For clarity, except as otherwise set forth in the footnotes to Table 3 below, GSK will be required to make a milestone payment only if the corresponding Development Milestone Event has actually occurred. For example, if Isis initiates a [***] for a second Indication without the need to conduct a [***], then Isis will not be entitled to receive the $[***] milestone payment for the [***].

GSK Comments (03/15/10)
For Discussion Purpose Only

Table 3

Development Milestone Events for a Licensed Product	**ID /Additional Programs – 1st Indication Column 1**	**ID /Additional Programs – 2nd Indication Column 2**
[***]†♣	[***]	[***]
[***]♣	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]††	[***]	[***]
[***]	[***]	[***]
[***]†††	[***]	[***]
[***]†††[***]	[***]	[***]
Total Development Milestone Payments per Collaboration Program	**[***]**	**[***]**

† For the ID/Additional Program for [***], the "*[***]*" Development Milestone Event (i) occurs when such Development Milestone Event is achieved in a [***] and (ii) shall also be deemed to have occurred when the "*[***]*" Development Milestone Event is achieved for the same Collaboration Program. For the ID/Additional Program that is the 6th Collaboration Program, the "*[***]*" Development Milestone Event (i) occurs when such Development Milestone Event is achieved in the [***] agreed to by the Parties and (ii) it shall also be deemed to have occurred when the "*[***]*" Development Milestone Event is achieved for the same Collaboration Program.

♣ For the ID/Additional Program for [***], if the [***] is completed and [***] has not been achieved but GSK desires to continue Development under such ID/Additional Program, then GSK may waive the condition that [***] be achieved in such [***] and the "*[***]*" Development Milestone Event for such ID/Additional Program will be deemed to have been achieved.

†† For clarity with respect to this Milestone Event, "*[***]*" by the applicable Regulatory Authority in [***] (or any other [***] such as [***] or the [***]) of the equivalent of [***] in [***] (or any other [***] such as [***] or the [***]) will satisfy the requirements for achievement of this Development Milestone Event.

††† For clarity with respect to this Milestone Event, "*[***]*" by the applicable Regulatory Authority in [***] (or any other [***] such as [***] or the [***]) of the equivalent of [***] in [***] (or any other [***] such as [***] or the [***]) will satisfy the requirements for achievement of this Development Milestone Event.

5.6.2. **Milestone Payments for Follow-On Compounds in ID/Additional Programs.** For each Collaboration Program that is an ID/Additional Program for which GSK has requested a Follow-On Compound under Section 1.4.5, (i) upon the designation of a Follow-On Compound as a Development Candidate, GSK will pay to Isis a milestone payment equal to [***] ($[***]), and (ii) when such Follow-On Compound first achieves a listed Milestone Event, by or on behalf of GSK or its Affiliates or Sublicensees, [***] percent ([***]%) of the milestone payments for such Development Milestone Event set forth in Table 3 above if such Follow-On Compound is the first Licensed Product under the applicable Option to achieve such Development Milestone Event, or in amounts that are [***] percent ([***]%) of the applicable milestone payments for such Development Milestone Event set forth in Table 3 above if such Follow-On Compound is not the first Licensed Product under the applicable Option to achieve such Development Milestone Event.

5.7. **Milestone Payments for Achievement of Sales Milestone Events**.

5.7.1. **Milestone Payments for First Achievement of Sales Milestone Event**. On a Collaboration Program-by-Collaboration Program basis, GSK will pay to Isis the applicable one-time milestone payments as set forth in Table 4 below (as determined by the type of Collaboration Program to achieve such event) after a Licensed Product that is part of such Collaboration Program first achieves the listed events (each, a ***"Sales Milestone Event"***), by or on behalf of GSK or its Affiliates or Sublicensees.

Table 4

Sales Milestones for each Licensed Product	Each Rare Disease Program	Each ID/ Additional Program
$[***] in worldwide Annual Net Sales	[***]	[***]
$[***] in worldwide Annual Net Sales	[***]	[***]
$[***] in worldwide Annual Net Sales	[***]	[***]
Total Sales Milestone Payments per Collaboration Program	**[***]**	**[***]**

5.8. **Limitations on Milestone Payments; Notice**.

5.8.1. Except as expressly set forth in Section 5.5.2, Section 5.6.2 and Section 1.6.2, each milestone set forth in Table 2, Table 3 and Table 4 above will be paid only once per Collaboration Program upon the first achievement of the Milestone Event, regardless of the number of Licensed Compounds, Follow-On Compounds or Licensed Products resulting under the Collaboration Program. So long as GSK has paid Isis the [***] milestone payment for the first Development Candidate in a Collaboration Program, GSK will not be required to pay Isis an additional [***] milestone payment under Table 2 or Table 3, as applicable, for a Back-Up Compound under the same Collaboration Program. If GSK is reimbursing Isis for all costs and expenses of advancing a Back-Up Compound beyond the stage of Development Candidate designation as described in Section 1.7.3 above, no milestone payments will be payable under Table 2 or Table 3, as applicable, with respect to such Back-Up Compound unless GSK later ceases to actively Develop the Development Candidate under the applicable Collaboration Program, in which case, if GSK or its Affiliate or Sublicensee achieves a Milestone Event with respect to such Back-Up Compound, GSK will make the applicable milestone payment only if such milestone payment has not been made by GSK to Isis with respect to the Development Candidate already.

5.8.2. Each time a Milestone Event is achieved under this ARTICLE 5, GSK will send Isis, or Isis will send GSK, as the case may be, a written notice thereof promptly (but in any event no later than ten (10) Business Days) following the date of achievement of such Milestone Event and such payment will be due within [***] ([***]) days of receipt by GSK of an invoice sent from Isis.

5.9. **Royalty Payments to Isis**.

5.9.1. **GSK Patent Royalty**. As partial consideration for the rights granted to GSK hereunder, GSK will pay to Isis royalties on Annual Net Sales of each Licensed Product sold by GSK, its Affiliates or Sublicensees, on a country-by-country basis and Licensed Product-by-Licensed Product basis, in the countries in which either (i) there is a Valid Claim within [***] Patents (or the foreign equivalent or counterpart of such [***] Patents) that is either licensed or assigned by Isis to GSK that Covers the [***] such Licensed Product or (ii) the data exclusivity period conferred by the applicable Regulatory Authority in such country with respect to such Licensed Product (such as in the case of an orphan drug), in each case in the amounts as follows (the "***GSK Patent Royalty***"). For purposes of clarification,

royalties are payable on Follow-On Products in the same manner as they are payable for Licensed Products containing the lead Development Candidates except that royalties on Licensed Products containing a Follow-On Compound will be paid at [***] percent ([***]%) of the rates set forth in Table 5 below otherwise applicable for Licensed Products; *provided*, *however*, if the Follow-On Product is the first Licensed Product to achieve First Commercial Sale for the applicable license Option, then GSK will pay [***] percent ([***]%) of the royalty rates set forth in Table 5 below for such Licensed Product, and any subsequent Licensed Products sold pursuant to the same license Option will be treated as Follow-On Products subject to the reduced royalty rate described in this Section 5.9.1.

(a) Subject to the provisions of this Section 5.9.1 and Section 5.9.2, GSK will pay to Isis the royalties at the percentages as described in Table 5 below:

Table 5

Annual Net Sales of each Licensed Product Worldwide	Royalty Rate
for the portion up to and including $[***]	[***]%
for the portion above $[***] and up to and including $[***]	[***]%
for the portion above $[***]	[***]%

(b) In the event any Combination Products are sold, royalties on such Combination Products will be calculated pursuant to the definition of "*Net Sales*" and "*Combination Products*" set forth in APPENDIX 1 to this Agreement.

(c) The royalty rates in Table 5 above are incremental rates, which apply only for the respective increment of worldwide Annual Net Sales described in the Annual Net Sales column. Thus, once a total worldwide Annual Net Sales figure is achieved for the Calendar Year, the royalties owed on any lower-tier portion of Annual Net Sales are not adjusted up to the higher-tier rate and the higher tier rate will only apply to the portion of the Annual Net Sales that are within the higher tier Annual Net Sales.

5.9.2. **Application of Royalty Rates**. All royalties set forth under Section 5.9.1 are subject to the provisions of this Section 5.9.2, and will be payable as follows, on a Licensed Product-by-Licensed Product and country-by-country basis:

(a) **Patent Royalty Term**. GSK's obligation to pay the GSK Patent Royalty above with respect to a Licensed Product and/or Combination Product will continue on a country-by-country and Licensed Product-by-Licensed Product basis from the date of First Commercial Sale of the Licensed Product until the later of the date of expiration of (i) the last Valid Claim within the [***] Patents (or the foreign equivalent or counterpart of such [***] Patents) that are either licensed or assigned

by Isis to GSK under this Agreement that Covers the [***] such Licensed Product sold in such country or (ii) the data exclusivity period conferred by the applicable Regulatory Authority in such country with respect to such Licensed Product (such as in the case of an orphan drug).

(b) **Know-How Royalty**. On a country-by-country and Licensed Product-by-Licensed Product basis, if GSK is not required to pay the GSK Patent Royalty, at any time during the period within [***] ([***]) years after the date of First Commercial Sale of such Licensed Product in such country, GSK will pay Isis a royalty at the rate of [***] percent ([***]%) of the GSK Patent Royalty rates as described in Section 5.9.1 above (the "***GSK Know-How Royalty***"); *provided, however*, if the Licensed Product is Covered by Third Party technology that is sublicensed by Isis to GSK under this Agreement and within the Licensed IP that bears a royalty or other financial obligation to such Third Party (including but not limited to any Isis Supported Pass-Through Costs) extending beyond such [***] ([***]) year term (such as manufacturing or formulation technology), GSK will, subject to Section 5.9.2(d) below, pay Isis a continuing royalty sufficient to cover Isis' obligations under such Third Party license or cease using such Third Party technology.

(c) **Reduction of Royalty for Competition from Generic Products**. On a country-by-country and Licensed Product-by-Licensed Product basis, if at any time during the Agreement Term one or more Third Parties are selling one or more Generic Products during the applicable Calendar Quarter, and such Generic Products taken in the aggregate have a market share (measured in number of prescriptions with the numerator of such fractional share being the Generic Products taken in the aggregate, and the denominator being the total of the Generic Products taken in the aggregate plus the Licensed Products taken in the aggregate, as provided by IMS) in such country of at least [***] percent ([***]%), then, subject to Section 5.9.2(d) below, GSK's obligation to pay royalties to Isis on Net Sales of the relevant Licensed Products in such country will be reduced to the amount which is [***] percent ([***]%) of the otherwise applicable GSK Patent Royalty rate under Section 5.9.1(a).

(d) **Limitation on Aggregate Reduction for GSK Royalties**. Notwithstanding anything in this Agreement to the contrary, on a Collaboration Program-by-Collaboration Program basis, in no event will Isis receive royalties for Annual Net Sales of Licensed Products sold by GSK or its Affiliates or Sublicensees, with respect to any Calendar Quarter, less than the sum of the Isis Supported Pass-Through Costs; provided such sum of the Isis Supported Pass-Through Costs is less than [***] percent ([***]%) of the Annual Net Sales of Licensed Products sold by GSK or its Affiliates or Sublicensees.

5.10. **Reverse Royalty Payments to GSK for Discontinued Products.**

5.10.1. **Reverse Royalty for Discontinued Products.** In the event that Isis or any of its Affiliates or Sublicensees Develops and Commercializes any Discontinued Product for which GSK has paid Isis the applicable [***] milestone payment, Isis will pay the following royalty payments to GSK set forth in Table 6 below, following the First Commercial Sale of a

Discontinued Product by Isis or its Affiliates or Sublicensees, on a country-by-country basis and Discontinued Product-by-Discontinued Product basis, for worldwide Annual Net Sales of all Discontinued Products within the relevant Collaboration Program ("***Reverse Royalties***") as follows:

Table 6

Development/Regulatory Status of Discontinued Product at time of reversion under this Agreement	Applicable Royalty Rate on worldwide Annual Net Sales of Discontinued Product
Discontinued Products for which GSK has paid Isis the applicable [***] milestone payment	[***]%
Discontinued Products for which GSK has (i) [***], *and* (ii) paid Isis the applicable [***] milestone payment	[***]%
[***]	[***]%
[***]	[***]%
[***]	[***]%

5.10.2. Applicable Royalty Provisions. In addition to this Section 5.10, the definition of Net Sales in APPENDIX 1 and the other provisions contained in this ARTICLE 5 governing payment of royalties from GSK to Isis will govern the payment of royalties from Isis to GSK under this Section 5.10, *mutatis mutandis*, including, without limitation, the provisions of Sections 5.9.2(a), 5.12, 5.13, 5.14, and 5.15.

5.11. Third Party Payment Obligations.

5.11.1. Isis In-License Agreements.

(a) Certain of the Licensed IP Controlled by Isis as of the Effective Date and during the Collaboration Term that are licensed to GSK under Section 4.1.1 are in-licensed or were acquired by Isis under agreements with Third Party licensors or sellers (such license or purchase agreements being the "***Isis In-License Agreements***"), and certain milestone and/or royalty payments may become payable by Isis to such Third Party under Isis In-License Agreements based on the Development and Commercialization of a Licensed Compound or Licensed Product by GSK under this Agreement. SCHEDULE 5.11.1 sets forth a list of Isis In-License Agreements related to Collaboration Programs existing as of the Effective Date. The Parties acknowledge that whether a milestone and/or royalty payment becomes payable by Isis to such Third Party licensor depends on the terms and conditions of the Isis In-License Agreement.

(b) Isis will be responsible for paying 100% of the Isis Supported Pass-Through Costs arising under any Isis In-License Agreements as they apply to any Licensed Compound or Licensed Product.

(c) GSK will be responsible for paying Isis 100% of the GSK Supported Pass-Through Costs arising under any Isis In-License Agreements as they apply to any Licensed Compound or Licensed Product.

5.11.2. Platform Blocking IP In-License Agreements. If GSK provides Isis with written notice of GSK's reasonable determination that a license to Platform Blocking IP is necessary to Develop and/or Commercialize a particular Licensed Product, then Isis will have the first right to negotiate with and obtain such a license from such Third Party. After obtaining such a Third Party license, Isis will include such Platform Blocking IP in any applicable license grant to GSK under Section 4.1.1 for such Licensed Product, and any financial obligations under such Third Party agreement will be paid solely by Isis as Isis-Supported Pass-Through Costs. If, however, Isis elects not to obtain such a license to such Third Party intellectual property, Isis will so notify GSK, and GSK may obtain such Third Party license and GSK may offset [***] percent ([***]%) of the payments applicable to such Licensed Product paid by GSK under such Third Party license against any milestone payments and Patent Royalty payments due to Isis under Section 5.5.1, Section 5.6.1 and/or Section 5.9.1 of this Agreement for such Licensed Product; *provided, that* in no event will Isis receive, with respect to any Calendar Quarter, less than the minimum royalty amount for such Licensed Product as stated in Section 5.9.2(d). GSK will have the right to carry forward and apply in future Calendar Quarters or Years any such unused offset to which GSK is entitled for such Licensed Product.

5.12. Payments.

5.12.1. Commencement. Beginning with the Calendar Quarter in which the First Commercial Sale for an applicable Licensed Product is made and for each Calendar Quarter thereafter, royalty payments will be made by GSK to Isis under this Agreement within [***] ([***]) days following the end of each such Calendar Quarter. Each royalty payment will be accompanied by a report, summarizing Net Sales for the applicable Licensed Product during the relevant Calendar Quarter and the calculation of royalties, if any, due thereon. Notwithstanding the foregoing, in the event that no royalties are payable in respect of a given Calendar Quarter, GSK will submit a written royalty report to Isis so indicating. In addition, beginning with the Calendar Quarter in which the First Commercial Sale for an applicable Licensed Product is made and for each Calendar Quarter thereafter, within [***] ([***]) Business Days following the end of each such Calendar Quarter, GSK will provide Isis a preliminary non-binding quarterly report estimating the total sales revenue of Licensed Products projected for such Calendar Quarter.

5.12.2. Mode of Payment. All payments under this Agreement will be (i) payable, in full, in U.S. dollars, regardless of the country(ies) in which sales are made, (ii) made by wire transfer of immediately available funds to an account designated by Isis in writing, and (iii) irrevocable, non-refundable, and non-creditable. For the purposes of computing Net Sales of Licensed Products sold in a currency other than U.S. dollars, such currency will be converted into U.S. dollars as calculated using the average exchange rates as calculated and utilized by GSK's group reporting system and published accounts.

5.12.3. Records Retention. Commencing with the First Commercial Sale of a Licensed Product, GSK will keep complete and accurate records pertaining to the sale of such Licensed Products for a period of three (3) Calendar Years after the year in which such sales occurred, and in sufficient detail to permit Isis to confirm the accuracy of the Net Sales or royalties paid by GSK hereunder.

5.13. Audits. During the Agreement Term and for a period of three (3) years thereafter, at the request and expense of Isis, GSK will permit an independent certified public accountant of nationally recognized standing appointed by Isis, and reasonably acceptable to GSK, at reasonable times and upon reasonable notice, but in no case more than once per Calendar Year thereafter, to examine such records as may be necessary for the sole purpose of verifying the calculation and reporting of Net Sales and the correctness of any royalty payment made under this Agreement for any period within the preceding three (3) years. The independent certified public accountant will disclose to Isis only the royalty amounts which the independent certified public accountant believes to be due and payable hereunder to the payee and will disclose no other information revealed in such audit. Any and all records of GSK examined by such independent certified public accountant will be deemed GSK's Confidential Information, which may not be disclosed by said independent certified public accountant to any Third Party or (except for the information expressly sought to be confirmed by Isis as set forth in this Section 5.13) to Isis. If, as a result of any inspection of the books and records of GSK, it is shown that GSK's payments under this Agreement were less than the royalty amount which should have been paid, then GSK will make all payments required to be

made by paying Isis the difference between such amounts to eliminate any discrepancy revealed by said inspection within sixty (60) days. If it is shown that GSK's payments under this Agreement were more than the royalty amount which should have been paid, then Isis will return that overpaid amount by paying GSK the difference between such amounts to eliminate any discrepancy revealed by said inspection within sixty (60) days. Isis will pay for such audits, except that in the event that GSK is found to have underpaid Isis by more than ten percent (10%) of the amount that should have been paid during the period in question, GSK will reimburse Isis' reasonable costs of the audit.

5.14. Taxes.

5.14.1. Sales or Other Transfers. The recipient of any transfer under this Agreement of Licensed IP, GSK Technology, Confidential Information, Licensed Compounds, or Licensed Products (including Discontinued Products), as the case may be, will be solely responsible for any sales, use, value-added, excise or other taxes applicable to such transfer.

5.14.2. Withholding Tax. The Parties acknowledge and agree that, under applicable laws in effect as of the Effective Date, GSK will not be required to withhold any taxes from the technology access fee under Section 5.2, election fees under Section 5.3, Option exercise fees under Section 5.4, milestone payments under Section 5.5 or Section 5.6, or any reimbursement payments for Developing Compounds under this Agreement (including under Section 1.7), (collectively, the "***Withholding-Free Payments***") in each case payable to Isis under this Agreement. Consequently, GSK agrees not to withhold any taxes from payment of the Withholding-Free Payments. Any tax paid or required to be withheld by GSK for the benefit of Isis on account of any royalties payable to Isis under this Agreement will be deducted from the amount of royalties or other payments otherwise due. GSK will secure and send to Isis proof of any such taxes withheld and paid by GSK for the benefit of Isis, and will, at Isis' request, provide reasonable assistance to Isis in recovering

such taxes. Isis warrants that Isis is a Delaware corporation as of the Effective Date and, prior to the payment of royalties by GSK hereunder, will be a resident for tax purposes in the US and that, as of such time, Isis will be entitled to relief from United Kingdom income tax under the terms of the double tax agreement between the UK and the US. Isis will notify GSK immediately in writing in the event that Isis ceases to be entitled to such relief. Pending receipt of formal certification from the UK Inland Revenue (the "***UK Tax Certification***"), GSK may pay royalty income under this Agreement to Isis by deducting tax at the applicable rate specified in the double tax treaty between the UK and US. After receipt of the UK Tax Certification, and so long as the UK Tax Certification remains current, GSK will not withhold any taxes from the payment of any royalties, unless GSK is advised such withholding is required under Applicable Law. Isis agrees to indemnify and hold harmless GSK against any loss, damage, expense or liability arising in any way from a breach of the above warranties or any future claim by a UK tax authority or other similar body alleging that GSK was not entitled to deduct withholding tax on such payments at source at the treaty rate, unless such loss, damage, expense or liability arises as a result of any legislative changes in the future, and except that Isis' indemnification obligation under this Section 5.14.2 will not apply to GSK's payment of the Withholding-Free Payments. GSK will indemnify and hold harmless Isis against any loss, damage, expense or liability arising in any way from a claim by a UK tax authority or other similar body alleging that the Withholding-Free Payments are subject to the withholding of taxes by GSK, unless such loss, damage, expense or liability arises as a result of any legislative changes in the future.

5.15. Interest. Any undisputed payments to be made hereunder that are not paid on or before the date such payments are due under this Agreement will bear interest at a rate per annum equal to the lesser of (i) the rate announced by Bank of America (or its successor) as its prime rate in effect on the date that such payment would have been first due plus [***] percent ([***]%) or (ii) the maximum rate permissible under applicable law. However, the interest on late payments shall not apply if the payment has been delayed by Isis (for instance due to invalid or late changes to bank details, non-compliance invoices, etc.) or if Isis has not responded to genuine questions or queries from GSK.

ARTICLE 6.
INTELLECTUAL PROPERTY

6.1. Ownership.

6.1.1. Isis Technology and GSK Technology. As between the Parties, Isis will own and retain all of its rights, title and interest in and to the Licensed Know-How and Isis Patents and GSK will own and retain all of its rights, title and interest in and to the GSK Know-How and GSK Patents, subject to any rights or licenses expressly granted by one Party to the other Party under this Agreement.

6.1.2. Collaboration Technology. As between the Parties, GSK will be the sole owner of any Know-How discovered, developed, invented or created solely by or on behalf of GSK and/or its Affiliates under this Agreement ("***GSK Collaboration Know-How***") and any Patent Rights that claim or cover GSK Collaboration Know-How ("***GSK Collaboration***

Patents" and together with the GSK Collaboration Know-How, the "***GSK Collaboration Technology***"), and will retain all of its rights, title and interest thereto, subject to any rights or licenses expressly granted by GSK to Isis under this Agreement. As between the Parties, Isis will be the sole owner of any Know-How discovered, developed, invented or created solely by or on behalf of Isis and/or its Affiliates ("***Isis Collaboration Know-How***") and any Patent Rights that claim or cover such Know-How ("***Isis Collaboration Patents***" and together with the Isis Collaboration Know-How, the "***Isis Collaboration Technology***"), and will retain all of its rights, title and interest thereto, subject to any rights or licenses expressly granted by Isis to GSK under this Agreement. Any Know-How that is discovered, developed, invented or created jointly under this Agreement by or on behalf of a Party or its Affiliates, on the one hand, and the other Party or such other Party's Affiliates, on the other hand ("***Jointly-Owned Collaboration Know-How***"), and any Patent Rights that claim or cover such Jointly-Owned Collaboration Know-How ("***Jointly-Owned Collaboration Patents***") and together with the Jointly-Owned Collaboration Know-How, the "***Jointly-Owned Collaboration Technology***"), will be owned jointly by GSK and Isis on an equal and undivided basis, including all rights, title and interest thereto, subject to any rights or licenses expressly granted by one Party to the other Party under this Agreement. Except as expressly provided in this Agreement, neither Party will have any obligation to account to the other for profits with respect to, or to obtain any consent of the other Party to license or exploit, Jointly-Owned Collaboration Technology by reason of joint ownership thereof, and each

Party hereby waives any right it may have under the laws of any jurisdiction to require any such consent or accounting. Each Party will promptly disclose to the other Party in writing, and will cause its Affiliates to so disclose, the discovery, development, invention or creation of any Jointly-Owned Collaboration Technology. The GSK Collaboration Patents, Isis Collaboration Patents and Jointly-Owned Collaboration Patents are collectively referred to herein as the "***Collaboration Patents***."

6.1.3. **Joint Patent Committee**.

(a) The Parties will establish a "***Joint Patent Committee***" or "***JPC***." The JPC will serve as the primary contacts and forum for discussion between the Parties with respect to intellectual property matters arising under this Agreement, and will cooperate with respect to the activities set forth in this ARTICLE 6. A strategy will be discussed with regard to prosecution and maintenance, defense and enforcement of Isis Product-Specific Patents, GSK Product-Specific Patents and Jointly-Owned Collaboration Patents that would be and/or are licensed to GSK under Section 4.1.1 in connection with a Collaboration Target or a Compound included in a Collaboration Program, defense against allegations of infringement of Third Party Patent Rights, and licenses to Third Party Patent Rights or Know-How, and any material change to any license to Third Party Patents Rights or Know-How in existence as of the Effective Date, in each case to the extent such matter would be reasonably likely to have a material impact on the Collaboration or the licenses granted hereunder. The Joint Patent Committee is established as of the Effective Date and will dissolve as a formal governing body upon the earlier of (i) the exercise or expiration of the Option with respect to the last Collaboration Program (ii) the Parties' mutual agreement or (iii) after the Collaboration Term, Isis' written

notice to GSK of its intention to disband and no longer participate in the JPC. Once Isis has provided such written notice, the JPC shall have no further obligations under this Agreement and the matters to be decided by the JPC shall be decided by the Parties.

(b) In addition, the Joint Patent Committee will be responsible for the determination of inventorship. The determination of inventorship will be made in accordance with United States patent laws. In case of a dispute in the Joint Patent Committee (or otherwise between Isis and GSK) over inventorship and, as a result, whether (i) any particular technology arising from the Collaboration is solely owned by one Party or the other or jointly owned by both Parties, or (ii) whether any particular Know-How is Isis Know-How, GSK Know-How or Jointly-Owned Collaboration Know-How, such dispute will be resolved pursuant to Section 6.1.3(d).

(c) The Joint Patent Committee will meet as often as agreed by them (and at least semi-annually if requested), via teleconference or videoconference or as otherwise agreed, to discuss matters arising out of the activities set forth in ARTICLE 6. To the extent reasonably requested by either Party, the Joint Patent Committee will solicit the involvement of more senior members of their respective legal departments (up to the most senior intellectual property attorney, where appropriate) with respect to critical issues, and may escalate issues to the JSC for input and resolution pursuant to Section 6.1.3(d). Each Party's representatives on the Joint Patent Committee will consider comments and suggestions made by the other in good faith. Notwithstanding anything in this Agreement to the contrary, neither Party will have the obligation to disclose information to the other Party through the Joint Patent Committee to the extent prohibited by obligation of confidentiality or protective order, that would result in loss of attorney-client or other relevant legal privilege, that constitutes proprietary manufacturing information or where the other Party has an actual or potential conflict of interest with respect to such information (e.g., where sharing such information would be reasonably likely to provide the recipient with an inappropriate commercial advantage).

(d) In the event the Joint Patent Committee cannot resolve any dispute arising thereunder, even with JSC's input, such dispute will be resolved by independent patent counsel not engaged or regularly employed in the past two (2) years by either Party and reasonably acceptable to both Parties to resolve such dispute. The decision of such independent patent counsel will be binding on the Parties with respect to the issue of inventorship. Expenses of such patent counsel will be shared equally by the Parties.

6.2. **Prosecution and Maintenance of Patents**.

6.2.1. **Patent Filings**. The Party responsible for Prosecution and Maintenance of any Patent Rights as set forth in Sections 6.2.2 and 6.2.3 will endeavor to obtain patent protection for Compounds and Licensed Products, if and as applicable, as it Prosecutes and Maintains its other patents Covering products in development, using counsel of its own choice but reasonably acceptable to the other Party, in such countries as the responsible Party sees fit.

6.2.2. **Isis Patents and GSK Patents**.

(a) Isis will control and be responsible for all aspects of the Prosecution and Maintenance of all Isis Patents, subject to Section 6.2.2(b) and Section 6.2.4.

(b) **Isis Patents After Exercise of Option**. After GSK has obtained the applicable license under Section 4.1.1 and following review and approval of a majority of the members of the Joint Patent Committee, Isis will assign to GSK all Isis Product-Specific Patents that Cover Licensed Compounds, Licensed Products and/or the Collaboration Target included in such Collaboration Program, and GSK will thereafter control and be responsible for all aspects of the Prosecution and Maintenance of all such Isis Product-Specific Patents, subject to Section 6.2.4.

(c) GSK will control and be responsible for all aspects of the Prosecution and Maintenance of all GSK Patents, subject to Section 6.2.4.

6.2.3. **Jointly-Owned Collaboration Patents**. The strategy and responsibility for Prosecution and Maintenance of all Jointly-Owned Collaboration Patents will be decided by the Joint Patent Committee.

6.2.4. **Other Matters Pertaining to Prosecution and Maintenance of Patents**.

(a) Each Party will keep the other Party informed through the Joint Patent Committee as to material developments with respect to the Prosecution and Maintenance of Isis Product-Specific Patents or GSK Orange Book Patents for which such Party has responsibility for Prosecution and Maintenance pursuant to Section 6.2.2, Section 6.2.3 or this Section 6.2.4, including, without limitation, by providing copies of material data as it arises, any office actions or office action response or other correspondence that such Party provides to or receives from any patent office, including notice of all interferences, reissues, re-examinations, oppositions or requests for patent term extensions, and all patent-related filings, and by providing the other Party the timely opportunity to have reasonable input into the strategic aspects of such Prosecution and Maintenance.

(b) If, during the Agreement Term, GSK intends to allow any GSK Product-Specific Patent with respect to which GSK is responsible for Prosecution and Maintenance to lapse or become abandoned without having first filed a continuation or substitution and such GSK Product-Specific Patent Covers any Discontinued Product, GSK will notify Isis of such intention at least sixty (60) days prior to the date upon which such Patent Right will lapse or become abandoned, and Isis will thereupon have the right, but not the obligation, to assume responsibility for the Prosecution and Maintenance of the claims within such GSK Product-Specific Patent that Covers the Discontinued Product at its own expense (subject to Section 6.3.1) with counsel of its own choice. For the avoidance of doubt, if Isis assumes responsibility for the Prosecution and Maintenance of any such GSK Product-Specific Patent under this Section 6.2.4(b), Isis will have no obligation to notify GSK of any intention of Isis to allow such GSK Product-Specific Patent to later lapse or become abandoned.

(c) If, during the Agreement Term, Isis intends to allow any Isis Product-Specific Patent with respect to which Isis is responsible for Prosecution and Maintenance to lapse or become abandoned without having first filed a continuation or substitution, then, if GSK has obtained a license to a Licensed Product under Section 4.1.1 (or still has the right to exercise its Option with respect to a Collaboration Program), then Isis will notify GSK of such intention at least sixty (60) days prior to the date upon which such Patent Right will lapse or become abandoned, and GSK will thereupon have the right, but not the obligation, to assume responsibility for the Prosecution and Maintenance thereof at its own expense (subject to Section 6.3.1) with counsel of its own choice. For the avoidance of doubt, if GSK assumes responsibility for the Prosecution and Maintenance of any such Isis Product-Specific Patent under this Section 6.2.4(c), GSK will have no obligation to notify Isis of any intention of GSK to allow such Isis Product-Specific Patent to later lapse or become abandoned.

(d) The Parties, through the Joint Patent Committee, will cooperate in good faith to determine if and when any divisional applications will be filed with respect to any Collaboration Patents or Isis Patents, and where a divisional patent application filing would be practical and reasonable, then such a divisional filing will be made and (i) GSK will have the first right to control the Prosecution and Maintenance of such claims within the Jointly-Owned Collaboration Patents or Isis Patents which solely Cover Licensed Compound or Licensed Product with respect to a Collaboration Program after exercise of an Option by GSK, or (ii) Isis will have the first right to control the Prosecution and Maintenance of such claims within the Collaboration Patents or Isis Patents which solely Cover Discontinued Products. If the Party responsible for Prosecution and Maintenance pursuant to this Section 6.2.4(d) is an owner or co-owner of such Collaboration Patent or Isis Patent, the other Party will have the step-in right described in Section 6.2.4(b) or Section 6.2.4(c), as applicable.

(e) If the Party responsible for Prosecution and Maintenance pursuant to Section 6.2.3 intends to allow such Jointly-Owned Collaboration Patent to lapse or become abandoned without having first filed a continuation or substitution, then such Party will notify the other Party of such intention at least sixty (60) days prior to the date upon which such Jointly-Owned Collaboration Patent will lapse or become abandoned, and such other Party will thereupon have the right, but not the obligation, to assume responsibility for the Prosecution and Maintenance thereof at its own expense (subject to Section 6.3.1) with counsel of its own choice, in which case the abandoning Party will, and will cause its Affiliates to, assign to the other Party (or, if such assignment is not possible, grant a fully-paid exclusive license in) all of their rights, titles and interests in and to such Jointly-Owned Collaboration Patents. For the avoidance of doubt, if a Party assumes responsibility for the Prosecution and Maintenance of any such Jointly-Owned Collaboration Patents under this Section 6.2.4(e), such Party will have no obligation to notify the other Party of any intention of such Party to allow such Jointly-Owned Collaboration Patents to later lapse or become abandoned.

(f) In addition, the Parties will consult, through the Joint Patent Committee, and take into consideration the comments of the other Party for all matters relating to interferences, reissues, re-examinations and oppositions with respect to those Patent Rights in which such other Party (i) has an ownership interest, (ii) has received a license thereunder in accordance with this Agreement, or (iii) may in the future, in accordance with this Agreement, obtain a license or sublicense thereunder.

6.3. **Patent Costs**.

6.3.1. **Jointly-Owned Collaboration Patents**. Isis and GSK will share equally the Patent Costs associated with the Prosecution and Maintenance of Jointly-Owned Collaboration Patents, unless the Parties otherwise agree; *provided that*, either Party may decline to pay its share of costs for filing, prosecuting and maintaining any Jointly-Owned Collaboration Patents in a particular country or particular countries, in which case the declining Party will, and will cause its Affiliates to, assign to the other Party (or, if such assignment is not possible, grant a fully-paid exclusive license in) all of their rights, titles and interests in and to such Jointly-Owned Collaboration Patents.

6.3.2. **Isis Patents and GSK Patents**. Except as set forth in Section 6.2.4 and Section 6.3.1, each Party will be responsible for all Patent Costs incurred by such Party prior to and after the Effective Date in all countries in the Prosecution and Maintenance of Patent Rights for which such Party is responsible under Section 6.2.

6.4. **Defense of Claims Brought by Third Parties**.

6.4.1. **Prior to Exercise of Option**. If a Third Party initiates a Proceeding claiming that any Patent Right owned by or licensed to such Third Party is infringed by the Development, Manufacture or Commercialization of any Compound (and related Licensed Product) being Developed under a Collaboration Program with respect to which GSK has not yet exercised its Option, Isis will have the first right, but not the obligation, to defend against such Proceeding at its sole cost and expense. In the event Isis elects to defend against such Proceeding, Isis will have the sole right to direct the defense and to elect whether to settle such claim; *provided*, if such Compound (and related Licensed Product) is being Developed under a Collaboration Program, then Isis will not settle such Proceeding without the prior written consent of GSK, not to be unreasonably withheld. In the event that Isis elects not to defend against such Proceeding within sixty (60) days after it first receives written notice of the actual initiation of such Proceeding, GSK will have the right, but not the obligation, to defend against such Proceeding at its sole cost and expense, which right GSK may exercise by providing Isis with a written notice thereof within thirty (30) days after GSK's receipt of Isis' notice of its election not to defend such Proceeding. After such exercise and thereafter, GSK will have the sole right to direct the defense of such Proceeding, including, without limitation, the right to settle such claim (but only with the prior written consent of Isis, not to be unreasonably withheld). In any event, the Party not defending such Proceeding will reasonably assist the Party defending such Proceeding and cooperate in any such litigation at the request and expense of the Party defending such Proceeding. Each Party may at its own expense and with its own counsel join any defense initiated and/or directed by the other Party under this Section 6.4.1. Each Party will provide the other Party with prompt written notice of the commencement of any such

Proceeding, or of any allegation of infringement of which such Party becomes aware and that is of the type described in this Section 6.4.1, and such Party will promptly furnish the other Party with a copy of each communication relating to the alleged infringement that is received by such Party.

6.4.2. **Following Exercise of Option**. If a Third Party initiates a Proceeding claiming that any Patent Right or Know-How owned by or licensed to such Third Party is infringed by the Development, Manufacture or Commercialization of any Licensed Product being Developed or Commercialized by GSK under a license granted under Section 4.1.1, GSK will have the first right, but not the obligation, to defend against any such Proceeding at its sole cost and expense. In the event GSK elects to defend against such Proceeding, GSK will have the sole right to direct the defense and to elect whether to settle such claim (but only with the prior written consent of Isis, not to be unreasonably withheld). In the event that GSK elects not to defend against a particular proceeding, then it will so notify Isis in writing within sixty (60) days after it first receives written notice of the actual initiation of such Proceeding, Isis will have the right, but not the obligation, to defend against such Proceeding at its sole cost and expense and thereafter Isis will have the sole right to direct the defense thereof, including, without limitation, the right to settle such claim (but only with the prior written consent of GSK, not to be unreasonably withheld). In any event, the Party not defending such Proceeding will reasonably assist the Party defending such Proceeding and cooperate in any such litigation at the request and expense of the Party defending such Proceeding. Each Party may at its own expense and with its own counsel join any defense initiated and/or directed by the other Party under this Section 6.4.2. Each Party will provide the other Party with prompt written notice of the commencement of any such Proceeding, or of any allegation of infringement of which such Party becomes aware and that is of the type described in this Section 6.4.2, and such Party will promptly furnish the other Party with a copy of each communication relating to the alleged infringement that is received by such Party.

6.4.3. **Discontinued Products**. If a Third Party initiates a Proceeding claiming that any Patent Right or Know-How owned by or licensed to such Third Party is infringed by the Development, Manufacture or Commercialization of any Discontinued Product, Isis will have the right, but not the obligation, to defend against and settle such Proceeding at its sole cost and expense; *provided*, *however*, if such Patent Right or Know-How also Covers the Development, Manufacture or Commercialization of any Licensed Product or Licensed Compound, GSK will have the sole right to direct the defense and to elect whether to settle such claim (but only with the prior written consent of Isis, not to be unreasonably withheld). In any event, GSK will reasonably assist Isis in defending such Proceeding and cooperate in any such litigation at the request and expense of Isis. Each Party may at its own expense and with its own counsel join any defense directed by the other Party. GSK will provide Isis with prompt written notice of the commencement of any such Proceedings, or of any allegation of infringement of which GSK becomes aware and that is of the type described in this Section 6.4.3, and GSK will promptly furnish Isis with a copy of each communication relating to the alleged infringement that is received by GSK.

6.4.4. **Interplay Between Enforcement of IP and Defense of Third Party Claims**. Notwithstanding the provisions of Sections 6.4.2 and 6.4.3, to the extent that a Party's defense against a Third Party claim of infringement under this Section 6.4 (excluding Section 6.4.1) would involve (i) the enforcement of the other Party's Know-How or Patent Rights, or (ii) the defense of an invalidity claim with respect to such other Party's Know-How or Patent Rights, then, in each case, the general concepts of Section 6.5 will apply to the enforcement of such other Party's Know-How or Patent Rights or the defense of such invalidity claim (*i.e.*, each Party has the right to enforce its own intellectual property, except that the relevant Commercializing Party will have the initial right, to the extent provided in Section 6.5, to enforce such Know-How or Patent Rights or defend such invalidity claim, and the other Party will have a step-in right, to the extent provided in Section 6.5, to enforce such Know-How or Patent Rights or defend such invalidity claim).

6.5. **Enforcement of Patents Against Competitive Infringement**.

6.5.1. **Duty to Notify of Competitive Infringement**. If either Party learns of an infringement, unauthorized use, misappropriation or threatened infringement by a Third Party to which such Party does not owe any obligation of confidentiality with respect to any Licensed Patents, Jointly-Owned Collaboration Technology, Licensed Know-How or, solely for purposes of Section 6.5.4, GSK Technology, by reason of the development, manufacture, use or commercialization of (i) a product that contains or consists of a compound as an active ingredient that is

substantially identical in structure, sequence or composition to a Compound in any Licensed Compound or Licensed Product being Developed or Commercialized under a license granted under Section 4.1.1 of this Agreement, or (ii) an Antisense product directed against a Collaboration Target ("***Competitive Infringement***"), such Party will promptly notify the other Party in writing and will provide such other Party with available evidence of such Competitive Infringement; *provided*, *however*, that for cases of Competitive Infringement under Section 6.5.6 below, such written notice will be given within ten (10) days.

6.5.2. **Following Exercise of Option**. For any Competitive Infringement with respect to any Licensed Compound (and any related Licensed Product) (except for any Discontinued Products) that occurs after GSK's exercise of an Option in reference to the Collaboration Program under which such Licensed Compounds were Developed, so long as part of such Proceeding GSK also enforces any GSK Orange Book Patents Controlled by GSK (including any Isis Product-Specific Patents assigned by Isis to GSK under this Agreement) being infringed that Cover such Licensed Compound (and any related Licensed Product), then GSK will have the first right, but not the obligation, to institute, prosecute, and control a Proceeding with respect thereto (including, without limitation, with respect to any defense or counterclaim brought in connection therewith that a GSK Orange Book Patent is invalid or unenforceable) by counsel of its own choice at its own expense, and Isis will have the right, at its own expense, to be represented in that action by counsel of its own choice, *however,* GSK will have the right to control such litigation, irrespective of whether Isis is represented by counsel of its own choice. If GSK fails to initiate a Proceeding within a period of ninety (90) days after receipt of written notice of such Competitive Infringement (subject to a ninety (90) day extension to conclude negotiations, if GSK has commenced good faith negotiations with an alleged infringer for elimination of such Competitive Infringement within such ninety (90) day period), Isis will have the right to initiate and control a Proceeding with respect to such Competitive Infringement by counsel of its own choice, and GSK will have the right to be represented in any such action by counsel of its own choice at its own expense.

6.5.3. **Joinder**.

(a) If one Party initiates a Proceeding in accordance with this Section 6.5, the other Party agrees to be joined as a party plaintiff where necessary and to give the first Party reasonable assistance and authority to file and prosecute the Proceeding. Subject to Section 6.5.4, the costs and expenses of the Party initiating the Proceeding under this Section 6.5.3(a) and the costs and expenses of the other Party incurred pursuant to this Section 6.5.3(a), will be borne by the Party initiating such Proceeding.

(b) If one Party initiates a Proceeding in accordance with this Section 6.5.3, the other Party may join such Proceeding as a party plaintiff where necessary for such other Party to seek lost profits with respect to such infringement.

6.5.4. **Share of Recoveries**. Any damages or other monetary awards recovered with respect to a Proceeding brought pursuant to this Section 6.5 will be shared as follows: (i) the amount of such recovery will first be applied to the Parties' reasonable out-of-pocket costs incurred in connection with such Proceeding (which amounts will be allocated pro rata if insufficient to cover the totality of such expenses); and then (ii) any remaining proceeds will be allocated between the Parties as follows: (A) if Isis initiates the Proceeding pursuant to Section 6.4.1 or Section 6.5.2, Isis will retain or receive such remaining proceeds; and (B) if GSK initiates the Proceeding pursuant to Section 6.5.2, GSK will receive and retain [***] [***].

6.5.5. **Settlement**. Neither Party may enter a settlement, consent judgment or other voluntary final disposition of a suit under this ARTICLE 6 that disclaims, limits the scope of, admits the invalidity or unenforceability of, or grants a license under a Patent Controlled by the other Party without first obtaining the written consent of the Party that Controls the relevant Patent.

6.5.6. **35 USC 271(e)(2) Infringement**. Notwithstanding anything to the contrary in this Section 6.5, solely with respect to Licensed Patents that have not been assigned to GSK under this Agreement for a Competitive Infringement under 35 USC 271(e)(2) the time period set forth in Section 6.5.2 during which a Party will have the initial right to bring a Proceeding will be shortened to a total of twenty five (25) days, so that, to the extent the other Party has the right, pursuant to such Sections, to initiate a Proceeding if the first Party does not initiate a Proceeding, such other Party will have such right if the first Party does not initiate a Proceeding within twenty five (25) days after such first Party's receipt of written notice of such Competitive Infringement.

6.6. **Other Infringement**.

6.6.1. **Jointly-Owned Collaboration Patents**. With respect to the infringement of a Jointly-Owned Collaboration Patent which is not a Competitive Infringement, the Parties will cooperate in good faith to bring suit together against such infringing party or the Parties

may decide to permit one Party to bring suit solely. Any damages or other monetary awards recovered with respect to a Proceeding brought pursuant to this Section 6.6.1 will be shared as follows: (i) the amount of such recovery will first be applied to the Parties' reasonable out-of-pocket costs incurred in connection with such Proceeding (which amounts will be allocated pro rata if insufficient to cover the totality of such expenses); and then (ii) (A) if the Parties jointly initiate a Proceeding pursuant to this Section 6.6.1, each Party will retain or receive fifty percent (50%) of such remaining proceeds; and (B) if only one Party initiates the Proceeding pursuant to Section 6.6.1, such Party will retain or receive such remaining proceeds.

6.6.2. **Patents Solely Owned by Isis**. Isis will retain all rights to pursue an infringement of any Patent Right solely owned by Isis which is other than a Competitive Infringement and Isis will retain all recoveries with respect thereto.

6.6.3. **Patents Solely Owned by GSK**. GSK will retain all rights to pursue an infringement of any Patent Right solely owned by GSK which is other than a Competitive Infringement and GSK will retain all recoveries with respect thereto.

6.7. **Patent Listing**.

6.7.1. **GSK's Obligations**. GSK will promptly, accurately and completely list, with the applicable Regulatory Authorities during the Agreement Term, all applicable GSK Orange Book Patents. Prior to such listings, the Parties will meet, through the Joint Patent Committee, to evaluate and identify all applicable Patent Rights, and GSK will have the right to review, where reasonable, original records relating to any invention for which Patent Rights are being considered by the Joint Patent Committee for any such listing. Notwithstanding the preceding sentence, GSK will retain final decision-making authority as to the listing of all applicable GSK Orange Book Patents for such Licensed Product (excluding Isis Core Technology Patents), regardless of which Party owns such GSK Orange Book Patent.

6.7.2. **Isis' Obligations**. Isis will promptly, accurately and completely list, with the applicable Regulatory Authorities during the Agreement Term, all applicable Isis Orange Book Patents. Prior to such listings, the Parties will meet, through the Joint Patent Committee, to evaluate and identify all applicable Patent Rights, and Isis will have the right to review, where reasonable, original records relating to any invention for which Patent Rights are being considered by the Joint Patent Committee for any such listing. Notwithstanding the preceding sentence, Isis will retain final decision-making authority as to the listing of all applicable Isis Orange Book Patents for such Discontinued Products, as applicable, regardless of which Party owns such Isis Orange Book Patents.

6.8. **CREATE Act**. Notwithstanding anything to the contrary in this ARTICLE 6, neither Party will have the right to make an election under the Cooperative Research and Technology Enhancement Act of 2004, 35 U.S.C. § 103(c)(2)-(c)(3) (the "***CREATE Act***") when exercising its rights under this ARTICLE 6 without the prior written consent of the other Party, which will not be unreasonably withheld, conditioned or delayed. With respect to any such permitted election, the Parties will use reasonable efforts to cooperate and coordinate their activities with respect to any submissions, filings or other activities in support thereof. The Parties acknowledge and agree that this Agreement is a "*joint research agreement*" as defined in the CREATE Act.

6.9. **Obligations to Third Parties**. Notwithstanding any of the foregoing, each Party's rights and obligations with respect to Licensed IP under this ARTICLE 6 will be subject to any Third Party rights and obligations existing as of the Effective Date.

6.10. **Additional Right and Exceptions**. Notwithstanding any provision of this ARTICLE 6, Isis retains the sole right to Prosecute and Maintain Isis Core Technology Patents and Isis Manufacturing and Analytical Patents during the Agreement Term and, except as provided in Section 6.5.2, to control any enforcement of Isis Core Technology Patents and Isis Manufacturing and Analytical Patents and will take the lead of such enforcement solely to the extent that the scope or validity of any Patent Rights Controlled by Isis and Covering the Isis Core Technology Patents or Isis Manufacturing and Analytical Patents is at risk.

6.11. **Patent Term Extension.** The Parties will cooperate with each other in gaining patent term extension wherever applicable to any Licensed Product. The Commercializing Party will determine which patents will be extended. All filings for such extension will be made by the Party to whom the patent is assigned; *provided*, *however*, that in the event that the Party to whom the patent is assigned elects not to file for an extension, such Party will (i) inform the other Party of its intention not to file, (ii) grant the other Party the right to file for such extension, and (iii) cooperate as necessary to assist the other Party in filing such extension.

6.12. **[***]**

6.13. **Rights for [***] Programs Limited to [***] Field.** Notwithstanding anything to the contrary in this ARTICLE 6, with respect to the [***] Program, GSK's rights under Sections 6.2, 6.3, 6.4, 6.5 and 6.6 are limited to the extent of the scope of the [***] Field.

ARTICLE 7.
REPRESENTATIONS AND WARRANTIES

7.1. **Representations and Warranties of Both Parties.** Each Party hereby represents and warrants to the other Party, as of the Effective Date, that:

7.1.1. such Party is duly organized, validly existing and in good standing under the laws of the jurisdiction of its incorporation or organization and has full corporate power and authority to enter into this Agreement and to carry out the provisions hereof;

7.1.2. such Party has taken all necessary action on its part to authorize the execution and delivery of this Agreement and the performance of its obligations hereunder;

7.1.3. this Agreement has been duly executed and delivered on behalf of such Party, and constitutes a legal, valid and binding obligation, enforceable against it in accordance with the terms hereof;

7.1.4. the execution, delivery and performance of this Agreement by such Party will not constitute a default under or conflict with any agreement, instrument or understanding, oral or written, to which it is a party or by which it is bound, or violate any law or regulation of any court, governmental body or administrative or other agency having jurisdiction over such Party;

7.1.5. no government authorization, consent, approval, license, exemption of or filing or registration with any court or governmental department, commission, board, bureau, agency or instrumentality, domestic or foreign, under any applicable laws, rules or regulations currently in effect, is or will be necessary for, or in connection with, the transaction contemplated by this Agreement or any other agreement or instrument executed in connection herewith, or for the performance by it of its obligations under this Agreement and such other agreements; and

7.1.6. it has not employed (and, to the best of its knowledge, has not used a contractor or consultant that has employed) and in the future will not employ (or, to the best of its knowledge, use any contractor or consultant that employs, provided that such Party may reasonably rely on a

representation made by such contractor or consultant) any Person debarred by the FDA (or subject to a similar sanction of EMEA or foreign equivalent), or any Person which is the subject of an FDA debarment investigation or proceeding (or similar proceeding of EMEA or foreign equivalent), in the conduct of the Pre-Clinical Studies or Clinical Studies of Compounds and related Licensed Products and its activities under each Collaboration Program.

7.2. **Representations and Warranties of Isis.** Isis hereby represents and warrants to GSK, as of the Effective Date, that:

7.2.1. Isis is the owner of, or otherwise has the right to grant, all rights and licenses (or sublicenses, as the case may be) it purports to grant to GSK with respect to the Licensed IP under this Agreement for all Collaboration Programs as they exist on the Effective Date;

7.2.2. to the best of its knowledge and belief, after due inquiry, Isis does not require any additional licenses or other intellectual property rights to conduct the identification, research, optimization and other Development activities contemplated to be conducted by Isis with respect to the Collaboration Programs as they exist on the Effective Date;

7.2.3. to the best of its knowledge and belief, after due inquiry, no written claims have been made against Isis alleging that (i) any of the Licensed Patents existing as of the Effective Date are invalid or unenforceable or (ii) the practice of the Licensed Patents in connection with a Collaboration Program infringes any intellectual property rights of a Third Party;

7.2.4. to the best of its knowledge and belief, there are no additional licenses (beyond those that would be granted to GSK under ARTICLE 4 upon the exercise of an Option) under any intellectual property that is owned or Controlled by Isis or its Affiliates as of the Effective Date that would be required in order for GSK to further Develop and Commercialize any Compounds that bind to the Collaboration Targets as of the Effective Date, in each case assuming the exercise by GSK of such Option on the Effective Date;

7.2.5. SCHEDULE 7.2.5(a), SCHEDULE 7.2.5(b) and SCHEDULE 7.2.5(c) set forth true, correct and complete lists of all Isis Core Technology Patents, Isis Manufacturing and Analytical Patents, and Product-Specific Patents that apply to the Collaboration Programs as such programs exist on the Effective Date, respectively, and indicates whether each such Patent is owned by Isis or licensed by Isis from a Third Party and if so, identifies the licensor or sublicensor from which the Patent is licensed;

7.2.6. SCHEDULE 5.11.1 sets forth true, correct and complete lists of all Isis In-License Agreements that Isis considers in good faith to be most relevant to the research, Development, Manufacture or Commercialization of Compounds as contemplated under the Collaboration Programs existing on the Effective Date (together with a description of all applicable Isis Supported Pass Through Costs); Isis is in compliance in all material respects with Isis In-License Agreements and is not in default or breach under any Isis In-License Agreements and, to the best of its knowledge and belief, there is no ground that would give any Third Party that is a party to any In-License Agreement the right to terminate such In-License Agreement, and to Isis' best knowledge and belief, none of such Third Parties are in default or breach under any Isis In-License Agreement;

7.2.7. SCHEDULE 7.2.7 is a complete and accurate list of all agreements that create Third Party Obligations, that Isis considers in good faith may materially limit or restrict the rights granted by Isis to GSK under this Agreement;

7.2.8. Isis has not granted to any Third Party rights under the Licensed IP to Develop, Manufacture or Commercialize any ASOs that bind to the Collaboration Targets existing as of the Effective Date, except Isis granted (i) Permitted Licenses, and (ii) Alnylam the right to practice the Isis Core Technology Patents for double-stranded RNAi under the Alnylam Agreement;

7.2.9. Isis owns or possesses adequate licenses or other rights to use all existing research tools that it uses or has used to identify the Compounds as of the Effective Date; and

7.2.10. Isis has not withheld from GSK any material data or any material correspondence, including to or from any Regulatory Authority, in Isis' possession as of the Effective Date that would be material and relevant to a reasonable assessment of the scientific, commercial, safety and regulatory liabilities and commercial value of the Collaboration Programs as listed on the Effective Date.

Further, except as otherwise set forth in the applicable Phase 2 PoC Data Package or schedule of exceptions provided to GSK in accordance with the procedures set forth below, the foregoing representations and warranties (other than those contained in Section 7.2.2 and Section 7.2.9) shall be deemed to be made by Isis to GSK upon the Bring Down Date (as defined below) with respect to each Collaboration Program, solely with respect to such Collaboration Program and solely with respect to the ASOs, Compounds, Collaboration Targets and Licensed IP applicable to such Collaboration Program as if the "Effective Date" is the Bring Down Date. If GSK has a good faith intention of exercising an Option prior to its receipt of the applicable Phase 2 PoC Data Package, GSK will notify Isis thereof, and Isis will have thirty (30) days following such notice to deliver to GSK a schedule of exceptions to the representations and warranties provided under this Section 7.2. For purposes of this Section 7.2, "***Bring Down Date***" will mean the date GSK receives from Isis (i) the applicable Phase 2 PoC Data Package, if GSK exercises the applicable Option after the applicable Collaboration Program completes the first Phase 2 PoC Trial; or (ii) the applicable Phase 2 PoC Data Package, to the extent available, delivered under Section 3.1.3, if GSK exercises the applicable Option before the applicable Collaboration Program completes the first Phase 2 PoC Trial.

7.3. **Isis Covenants**. Isis hereby covenants to GSK that:

7.3.1. during the Term, Isis will maintain and not breach any agreements with Third Parties that provide a grant of rights from such Third Party to Isis that are Controlled by Isis and are licensed or become subject to a license from Isis to GSK under this Agreement;

7.3.2. all employees of Isis performing Development activities hereunder on behalf of Isis will be obligated to assign all right, title and interest in and to any inventions developed by them, whether or not patentable, to Isis or such Affiliate, respectively, as the sole owner thereof;

7.3.3. Isis will, as appropriate, hire and maintain sufficient staff and management to meet its Commercially Reasonable Efforts in order to support and conduct all the Collaboration Programs hereunder in a timely fashion;

7.3.4. except as permitted under Section 2.1.2, it will not during the Agreement Term grant any right or license to any Third Party that would conflict or interfere with any of the rights or licenses granted to GSK hereunder, or would encumber the Isis Patents that apply to the rights or licenses granted to GSK hereunder including, without limitation, any liens, mortgages, security interests or another similar interest that would give the holder the right to convert the interest into ownership of such Isis Patent(s);

7.3.5. in the event that Isis has knowledge, at any time during the Agreement Term of any settled, pending or threatened (in writing) claim or lawsuit or legal proceeding of a Third Party against Isis alleging that any Isis Patent is invalid or unenforceable, or Isis or GSK's practices of such Isis Patent(s) under this Agreement infringes or misappropriates in part or in whole the intellectual property or intellectual property rights of such Third Party, Isis will promptly inform GSK in writing of the same; and

7.3.6. Isis will perform its activities pursuant to this Agreement in compliance with good laboratory and clinical practices and cGMP, in each case as applicable under the laws and regulations of the country and the state and local government wherein such activities are conducted, and with respect to the care, handling and use in Development activities hereunder of any non-human animals by or on behalf of Isis, will at all times comply with all applicable federal, state and local laws, regulations and ordinances and the guiding principles of the "*3R's*", namely, wherever reasonably possible, reducing the number of animals used, replacing animals with non-animal methods and refining the research techniques used for the proper care, handling and use of animals in pharmaceutical research and development activities, subject to GSK's reasonable right to conduct reasonable inspections (but not to audit) with advance notice; and will promptly and in good faith undertake reasonable corrective steps and measures to remedy the situation to the extent that any significant deficiencies in complying with the "*3R's*" or applicable law or regulation are identified as the result of any such inspection.

7.4. **GSK Covenants.** GSK hereby covenants to Isis that GSK will perform its activities pursuant to this Agreement in compliance with good laboratory and clinical practices and cGMP, in each case as applicable under the laws and regulations of the country and the state and local government wherein such activities are conducted, and with respect to the care, handling and use in Development activities hereunder of any non-human animals by or on behalf of GSK; will at all times comply (and will ensure compliance by any of its subcontractors or Affiliates) with all applicable federal, state and local laws, regulations and ordinances and the guiding principles of the "*3R's*", namely, wherever reasonably possible, reducing the number of animals used, replacing animals with non-animal methods and refining the research techniques used for the proper care, handling and use of animals in pharmaceutical research and development activities, subject to Isis' reasonable right to conduct reasonable inspections (but not to audit) with advance notice; and will promptly and in good faith undertake reasonable corrective steps and measures to remedy the situation to the extent that any significant deficiencies in complying with the "*3R's*" or applicable law or regulation are identified as the result of any such inspection.

7.5. **DISCLAIMER.** EXCEPT AS OTHERWISE EXPRESSLY SET FORTH IN THIS AGREEMENT, NEITHER PARTY NOR ITS AFFILIATES MAKES ANY REPRESENTATION OR EXTENDS ANY WARRANTY OF ANY KIND, EITHER EXPRESS OR IMPLIED, INCLUDING, BUT NOT LIMITED TO, ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR ANY WARRANTY THAT ANY PATENT RIGHTS LICENSED TO THE OTHER PARTY HEREUNDER ARE VALID OR ENFORCEABLE OR THAT THEIR EXERCISE DOES NOT INFRINGE OR MISAPPROPRIATE ANY PATENT RIGHTS OR OTHER INTELLECTUAL PROPERTY RIGHTS OF THIRD PARTIES. GSK AND ISIS UNDERSTAND THAT THE COMPOUNDS ARE THE SUBJECT OF ONGOING CLINICAL RESEARCH AND DEVELOPMENT AND THAT NEITHER PARTY CAN ASSURE THE SAFETY, USEFULNESS OR COMMERCIAL OR TECHNICAL VIABILITY OF RESULTING DEVELOPMENT CANDIDATES, LICENSED COMPOUNDS, AND/OR LICENSED PRODUCTS.

ARTICLE 8.
INDEMNIFICATION; INSURANCE

8.1. **Indemnification by GSK**. GSK will indemnify, defend and hold harmless Isis and its Affiliates, and its or their respective directors, officers, employees and agents, from and against any and all liabilities, damages, losses, costs and expenses including, but not limited to, the reasonable fees of attorneys and other professionals (collectively "***Losses***") arising out of or resulting from any and all Third Party suits, claims, actions, proceedings or demands ("***Claims***") based upon:

8.1.1. the negligence, recklessness or wrongful intentional acts or omissions of GSK and/or its Affiliates and its or their respective directors, officers, employees and agents, in connection with GSK's performance of its obligations or exercise of its rights under this Agreement;

8.1.2. any breach of any representation or warranty or express covenant made by GSK under ARTICLE 7 or any other provision under this Agreement;

8.1.3. the Development or Manufacturing activities that are conducted by and/or on behalf of GSK or its Affiliates or Sublicensees (which will exclude any Development or Manufacturing activities that are conducted by and/or on behalf of Isis pursuant to this

Agreement), including handling and storage and manufacture by and/or on behalf of GSK or its Affiliates or Sublicensees of any Licensed Compounds or Licensed Product for the purpose of conducting Development or Commercialization by or on behalf of GSK or its Affiliates or Sublicensees; or

8.1.4. the Commercialization by or on behalf of GSK or its Affiliates or Sublicensees of any Licensed Product pursuant to the exercise by GSK of the relevant Option;

except, in each case above, to the extent such Claim arose out of or resulted from or is attributable to any acts or omissions of Isis and/or its Affiliates, licensees, Sublicensees or contractors, and its or their respective directors, officers, employees and agents, for which Isis is required to indemnify GSK pursuant to Section 8.2.

8.2. **Indemnification by Isis**. Isis will indemnify, defend and hold harmless GSK and its Affiliates, and its or their respective directors, officers, employees and agents, from and against any and all Losses arising out of or resulting from any and all Claims based upon:

8.2.1. the negligence, recklessness or wrongful intentional acts or omissions of Isis and/or any of its Affiliates and/or its or their respective directors, officers, employees and agents, in connection with Isis' performance of its obligations or exercise of its rights under this Agreement;

8.2.2. any breach of any representation or warranty or express covenant made by Isis under ARTICLE 7 or any other provision under this Agreement;

8.2.3. the discovery, Development or Manufacturing activities conducted by or on behalf of Isis (which will exclude any Development or Manufacturing activities conducted by or on behalf of GSK pursuant to this Agreement), including the storage and handling and manufacture by and/or on behalf of Isis and/or its Affiliates and/or its Sublicensees or subcontractors of any Compounds for the purpose of Development or Commercialization by or on behalf of Isis or GSK under this Agreement; or

8.2.4. the Commercialization of any Discontinued Products by or on behalf of Isis and/or its Affiliates or Sublicensees;

except, in each case above, to the extent such Claim arose out of or resulted from or is attributable to any acts or omissions of GSK and/or its Affiliates, licensees, Sublicensees or contractors and its or their respective directors, officers, employees and agents for which GSK is required to indemnify Isis pursuant to Section 8.1.

8.3. **Procedure**. In the event that any Person entitled to indemnification under Section 8.1 or Section 8.2 (an "***Indemnitee***") is seeking such indemnification, such Indemnitee will (i) inform, in writing, the indemnifying Party of a Claim as soon as reasonably practicable after such Indemnitee receives notice of such Claim, (ii) permit the indemnifying Party to assume direction and control of the defense of the Claim (including the sole right to settle it at the sole discretion of the indemnifying Party, *provided that* such settlement or compromise does not admit any fault or negligence on the part of the Indemnitee, or impose any obligation on, or otherwise materially adversely affect, the Indemnitee or other Party), (iii) cooperate as reasonably requested (at the

expense of the indemnifying Party) in the defense of the Claim, and (iv) undertake reasonable steps to mitigate any loss, damage or expense with respect to the Claim. The provisions of Section 6.4 will govern the procedures for responding to a Claim of infringement described therein. Notwithstanding anything in this Agreement to the contrary, the indemnifying Party will have no liability under Section 8.1 or 8.2, as the case may be, with respect to Claims settled or compromised by the Indemnitee without the indemnifying Party's prior written consent.

8.4. **Insurance**.

8.4.1. **Isis' Insurance Obligations**. Isis will maintain, at its cost, reasonable insurance against liability and other risks associated with its activities contemplated by this Agreement, including but not limited to its clinical trials and its indemnification obligations herein, in such amounts and on such terms as are customary for prudent practices for biotech companies of similar size and with similar resources in the pharmaceutical industry for the activities to be conducted by it under this Agreement taking into account the scope of development of products, *provided, that*, at a minimum, Isis will maintain, in force from thirty (30) days prior to enrollment of the first patient in a Clinical Study, at its sole cost, a clinical trials/product liability insurance policy providing coverage of at least [***] Dollars ($[***]) per claim and annual aggregate and, provided further that such coverage is increased to at least [***] Dollars ($[***]) at least thirty (30) days before Isis initiates the First Commercial Sale of any Discontinued Product hereunder. Isis will furnish to GSK evidence of such insurance upon request.

8.4.2. **GSK's Insurance Obligations**. GSK hereby represents and warrants to Isis that it is self-insured against liability and other risks associated with its activities and obligations under this Agreement in such amounts and on such terms as are customary for prudent practices for large companies in the pharmaceutical industry for the activities to be conducted by GSK under this Agreement. GSK will furnish to Isis evidence of such self-insurance upon request.

8.5. **LIMITATION OF CONSEQUENTIAL DAMAGES**. EXCEPT FOR CLAIMS OF A THIRD PARTY WHICH ARE SUBJECT TO INDEMNIFICATION UNDER THIS ARTICLE 8 OR AS OTHERWISE EXPRESSLY STATED IN THIS AGREEMENT, NEITHER ISIS NOR GSK, NOR ANY OF THEIR AFFILIATES OR SUBLICENSEES WILL BE LIABLE TO THE OTHER PARTY TO THIS AGREEMENT OR ITS AFFILIATES OR ANY OF THEIR SUBLICENSEES FOR ANY INCIDENTAL, CONSEQUENTIAL, SPECIAL, PUNITIVE OR OTHER INDIRECT DAMAGES OR LOST OR IMPUTED PROFITS OR ROYALTIES, LOST DATA OR COST OF PROCUREMENT OF SUBSTITUTE GOODS OR SERVICES, WHETHER LIABILITY IS ASSERTED IN CONTRACT, TORT (INCLUDING NEGLIGENCE AND STRICT PRODUCT LIABILITY), INDEMNITY OR CONTRIBUTION, AND IRRESPECTIVE OF WHETHER THAT PARTY OR ANY REPRESENTATIVE OF THAT PARTY HAS BEEN ADVISED OF, OR OTHERWISE MIGHT HAVE ANTICIPATED THE POSSIBILITY OF, ANY SUCH LOSS OR DAMAGE.

ARTICLE 9.
TERM; TERMINATION

9.1. **Agreement Term; Expiration.** This Agreement will be effective as of the Effective Date and will continue in force and effect until expiration as described in this Section 9.1, unless earlier terminated pursuant to the other provisions of this ARTICLE 9, and will expire as follows:

9.1.1. on a Licensed Product-by-Licensed Product and country-by-country basis, on the date of expiration of all payment obligations by the Commercializing Party under this Agreement with respect to such Licensed Product (including Discontinued Products) in such country;

9.1.2. in its entirety upon the expiration of all payment obligations under this Agreement with respect to the last Licensed Product (including Discontinued Products) in all countries pursuant to Section 9.1.1; and

9.1.3. where GSK declines to exercise a given Option on or before the applicable Option Deadline for a given Collaboration Program, on a Collaboration Program-by-Collaboration Program basis, the rights and obligations of each Party with respect to such Collaboration Program will terminate upon expiration of the Option Deadline with respect to the relevant Collaboration Program.

9.1.4. the period from the Effective Date until the date of expiration of this Agreement or as the case may be, until the date of expiration of this Agreement in part with respect to a given Licensed Product pursuant to this Section 9.1 will be the "***Agreement Term***."

9.1.5. **Effect of Expiration of the Agreement Term.** Following the expiration of the Agreement Term with respect to a Licensed Product (including Discontinued Products) in a country pursuant to Section 9.1.1, (i) if GSK is the Commercializing Party, the license granted to GSK pursuant to Section 4.1.1 with respect to such Licensed Product will convert to an exclusive, fully paid and royalty-free, right and license, with the right to grant sublicenses (as set forth in Section 4.1.2), under all of Isis' rights in and to the Know-How within the Licensed IP, solely as necessary to continue to Develop, Manufacture and Commercialize such Licensed Product in such country, for so long as it continues to do so; (ii) if Isis is the Commercializing Party, the license granted to Isis pursuant to Section 10.1, with respect to such Discontinued Product, will convert to an exclusive, fully paid and royalty-free right and license, with the right to grant sublicenses, under all of GSK's rights in and to the Know-How within the GSK Technology, solely as necessary to continue to Develop, Manufacture and Commercialize such Discontinued Product in such country, for so long as it continues to do so; and (iii) any remaining exclusivity obligation under ARTICLE 2 will no longer apply to bind or restrict either Party or its Affiliates with respect to the gene target against which such Licensed Product, or Discontinued Product, as the case may be, is directed.

9.2. **Termination of the Agreement**.

9.2.1. **GSK's Right to Terminate.** At any time during the Agreement Term, but following payment by GSK of the up-front payment described in Section 5.2, GSK will be entitled to terminate this Agreement in its entirety or in part on a Licensed Product-by-Licensed Product, Collaboration Program-by-Collaboration Program basis by providing ninety (90) days' written notice to Isis of such termination; *provided, however*, with respect to each Voluntarily Terminated Collaboration Program (as defined below) GSK will pay Isis an

amount equal to [***] percent ([***]%) of the milestone payment associated with the next Development Milestone Event that is a [***] Development Milestone Event unachieved as of the date of such notice (such payment, the "***Termination Payment***"). If Isis enters into a licensing or collaboration agreement with a Third Party for such Voluntarily Terminated Collaboration Program within [***] ([***]) months after the effective date of GSK's termination of such Voluntarily Terminated Collaboration Program, then Isis shall pay GSK an amount equal to the applicable Termination Payment in full within ten (10) days. For purposes of this Section 9.2.1, a "***Voluntarily Terminated Collaboration Program***" means a Collaboration Program terminated by GSK under this Section 9.2.1 meeting the following conditions:

(a) the Collaboration Program is not focused on [***] or [***];

(b) GSK terminated such Collaboration Program after Sanctioned Target stage but prior to GSK's exercise of the applicable Option for such Collaboration Program;

(c) at the time of such termination, Isis had initiated Development work past the Sanctioned Target stage for such Collaboration Program and in Developing such Collaboration Program Isis spent at least an amount equal to (i) $[***] *plus* (ii) [***] percent ([***]%) of the aggregate amount of the [***] and [***] paid by GSK to Isis pursuant to Section 5.3 and Section 5.5 or 5.6, as demonstrated by documentation provided to GSK;

(d) solely with respect to [***], such terminated Collaboration Program was the last Collaboration Program focused on [***]; and

(e) solely with respect to the [***] Program, such terminated Collaboration Program was the last [***] Program subject to an Option under this Agreement.

Subject to Section 9.3.4 and Section 9.3.5, immediately following such termination notice date, GSK's obligations under Section 5.5 through Section 5.9 will cease. Notwithstanding the foregoing, in the event GSK believes in good faith that there are safety concerns with respect to a Licensed Product or a Collaboration Program, which concerns merit the immediate termination of Licensed Product or Collaboration Program, GSK will have the right to terminate this Agreement with respect to such Licensed Product or Collaboration Program immediately upon written notice to Isis and without such ninety (90) day notice period for termination [***].

9.2.2. **Termination for Material Breach**.

(a) If either Party (the "***Non-Breaching Party***") believes that the other Party (the "***Breaching Party***") is in material breach of this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under Section 1.4 or Section 4.3, which is governed by Section 9.2.3 below), then the Non-Breaching Party may deliver notice of such material breach to the Breaching Party. In such notice, the Non-Breaching Party will identify the actions or conduct that it wishes such Breaching Party to take for an acceptable and prompt cure of such breach (or will otherwise state its good-faith belief that such breach is incurable); *provided,*

however, that such identified actions or conduct will not be binding upon the Breaching Party with respect to the actions that it may need to take to cure such breach. If the breach is curable, the Breaching Party will have ninety (90) days to either cure such breach (except to the extent such breach involves the failure to make a payment when due, which breach must be cured within thirty (30) days following such notice) or, if a cure cannot be reasonably effected within such ninety (90) day period, to deliver to the Non-Breaching Party a plan for curing such breach which is reasonably sufficient to effect a cure within a reasonable period. If the Breaching Party fails to (a) cure such breach within the ninety (90) day or thirty (30) day period, as applicable, or (b) use Commercially Reasonable Efforts to carry out the plan and cure the breach, the Non-Breaching Party may terminate this Agreement in its entirety if such breach relates to this Agreement in its entirety, or in relevant part if such breach does not relate to this Agreement in its entirety, by providing written notice to the Breaching Party.

(b) The termination right set forth in this Section 9.2.2 will be in addition to the provisions of Section 9.2.3 and Section 9.2.4.

9.2.3. Termination for Failure to Use Commercially Reasonable Efforts.

(a) If Isis, in GSK's reasonable determination, fails to use Commercially Reasonable Efforts in the activities contemplated in Section 1.4 above, GSK will notify Isis and, within thirty (30) days thereafter, Isis and GSK will meet and confer to discuss and resolve the matter in good faith, and attempt to devise a mutually agreeable plan to address any outstanding issues related to Isis' use of Commercially Reasonable Efforts in Section 1.4. Following such a meeting, if Isis fails to use Commercially Reasonable Efforts as contemplated by Section 1.4, then subject to Section 9.2.3(c), Section 9.2.3(d), and Section 9.2.4 below, GSK will have the right, at its sole discretion, to terminate this Agreement in whole or in part on a Collaboration Program-by-Collaboration Program basis.

(b) If GSK, in Isis' reasonable determination, fails to use Commercially Reasonable Efforts under Section 4.3 above, Isis will notify GSK and, within thirty (30) days thereafter, Isis and GSK will meet and confer to discuss and resolve the matter in good faith, and attempt to devise a mutually agreeable plan to address any outstanding issues related to GSK's use of Commercially Reasonable Efforts in Section 4.3. Following such a meeting, if GSK fails to use Commercially Reasonable Efforts as contemplated by Section 4.3, then subject to Section 9.2.3(c), Section 9.2.3(d), and Section 9.2.4 below, Isis will have the right, at its sole discretion, to terminate this Agreement in part on a Licensed Product-by-Licensed Product basis.

(c) Notwithstanding the foregoing, this Agreement will not so terminate unless (x) the Breaching Party is given ninety (90) days prior written notice by the Non-Breaching Party of the Non-Breaching Party's intent to terminate, stating the reasons and justification for such termination and recommending steps which the Breaching Party should take, and (y) the Breaching Party or its Sublicensee has not used good-faith Commercially Reasonable Efforts during the ninety (90) day period following such notice to diligently pursue a cure of such material breach or exercised its rights under Section 9.2.4.

(d) This Section 9.2.3 and Section 9.3 set forth the Non-Breaching Party's sole and exclusive remedy for the Breaching Party's breach of its obligation to use Commercially Reasonable Efforts.

9.2.4. Disputes Regarding Material Breach. Notwithstanding the foregoing, if the Breaching Party in Section 9.2.2 or Section 9.2.3 disputes in good faith the existence, materiality, or failure to cure of any such breach which is not a payment breach, and provides notice to the Non-Breaching Party of such dispute within such ninety (90) day period or such other reasonable cure period, as applicable, the Non-Breaching Party will not have the right to terminate this Agreement in accordance with Section 9.2.2 or Section 9.2.3, as applicable, unless and until it has been determined in accordance with Section 12.1 that this Agreement was materially breached by the Breaching Party and the Breaching Party fails to cure such breach within the allowed cure period following such determination. It is understood and acknowledged that during the pendency of such dispute, all the terms and conditions of this Agreement will remain in effect and the Parties will continue to perform all of their respective obligations hereunder.

9.2.5. Termination for Insolvency.

(a) Either Party may terminate this Agreement if, at any time, the other Party files in any court or agency pursuant to any statute or regulation of any state or country a petition in bankruptcy or insolvency or for reorganization or for an arrangement or for the appointment of a receiver or trustee of the Party or of substantially all of its assets; or if the other Party proposes a written agreement of composition or extension of substantially all of its debts; or if the other Party will be served with an involuntary petition against it, filed in any insolvency proceeding, and such petition will not be dismissed within ninety (90) days after the filing thereof; or if the other Party will propose or be a party to any dissolution or liquidation; or if the other Party will make an assignment of substantially all of its assets for the benefit of creditors.

(b) All rights and licenses granted under or pursuant to any section of this Agreement are and will otherwise be deemed to be for purposes of Section 365(n) of Title 11, United States Code (the "***Bankruptcy Code***") licenses of rights to "intellectual property" as defined in Section 101(56) of the Bankruptcy Code. The Parties will retain and may fully exercise all of their respective rights and elections under the Bankruptcy Code. Upon the bankruptcy of any Party, the non-bankrupt Party will further be entitled to a complete duplicate of, or complete access to, any such intellectual property, and such, if not already in its possession, will be promptly delivered to the non-bankrupt Party, unless the bankrupt Party elects to continue, and continues, to perform all of its obligations under this Agreement.

9.3. Consequences of Termination of the Agreement. In the event of a termination of this Agreement by a Party in its entirety or on a Collaboration Program-by-Collaboration Program basis or Licensed Product-by-Licensed Product basis, as the case may be, the following terms will apply to any such termination, but only to the extent of any such termination (*i.e.*, in part or in its entirety):

9.3.1. **Special Consequences for Termination by GSK.** In the event of a termination of this Agreement either in its entirety or on a Collaboration Program-by-Collaboration Program basis by GSK pursuant to Section 9.2.2, 9.2.3 or 9.2.5, then:

(a) the licenses granted by GSK to Isis under this Agreement will terminate, except that Isis, its Affiliates and Sublicensees may sell any remaining inventory of such Discontinued Products obtained from GSK pursuant to Section 10.1 over a period of no greater than twelve (12) months after the effective date of such termination; and Isis will pay GSK royalties in accordance with Section 5.10 on the Net Sales of such inventory of such Discontinued Products;

(b) except as explicitly set forth in this Section 9.3.1, Section 9.3.3, 9.3.4 or 9.2.5 Isis will have no further rights and GSK will have no further obligations with respect to the applicable terminated Collaboration Program(s);

(c) notwithstanding anything contained herein to the contrary, for each Collaboration Program for which GSK has not exercised its Option, GSK will have and Isis hereby grants, with respect to each Collaboration Program terminated under Section 9.2.2 or Section 9.2.3, the exclusive licenses granted to GSK under Section 4.1.1 with respect to the Licensed Compounds and Licensed Products under such Collaboration Program at the Option exercise payment, milestones, and royalties that are set forth in ARTICLE 5 (subject to Section 9.3.1(e) and Section 9.3.1(f) below);

(d) Isis will perform its obligations under Section 4.2.1 with respect to the applicable terminated Collaboration Program(s);

(e) GSK will not be required to pay milestone payments for any Development Milestone Event up to and including the [***] with respect to the applicable terminated Collaboration Programs (*i.e.*, including the milestone payment for the [***]); *provided, however*, GSK will be required to pay Isis the full amount of the (i) milestone payments for any achieved Development Milestone Event after the [***], (ii) milestone payments for any achieved Sales Milestone Events, (iii) Option exercise payments, and (iv) royalties, with respect to the applicable terminated Collaboration Programs, in each case in accordance with ARTICLE 5; and

(f) As a result of such termination, Isis will pay GSK on a quarterly basis within [***] days of Isis' receipt of GSK's invoice, an amount equal to the product of (i) the [***], *minus* the [***], *multiplied by* (ii) [***]percent ([***]%). The Parties will enter into any agreements required to address clinical safety, clinical trial responsibilities and regulatory matters to comply with applicable laws and regulations.

The Parties acknowledge and agree that the special consequences set forth in this Section 9.3.1 constitute a genuine and reasonable good faith pre-estimate of the damages that will be suffered by GSK upon the occurrence of any termination by GSK under Section 9.2.2, 9.2.3 or 9.2.5 and will not be characterized as or deemed to be a penalty.

9.3.2. **Special Consequences for Termination by Isis or Voluntary Termination by GSK.** In the event of a termination of this Agreement either in its entirety or on a Licensed Product-by-Licensed Product basis by Isis pursuant to Section 9.2.2 or Section 9.2.3, or by GSK pursuant to Section 9.2.1, then

(a) the licenses granted by Isis to GSK under this Agreement will terminate and GSK, its Affiliates and Sublicensees will cease selling all Licensed Products that are the subject of such termination; *provided that* GSK, its Affiliates and Sublicensees will have the right to sell any remaining inventory of such Licensed Products over a period of no greater than [***] ([***]) months after the effective date of such termination and GSK will pay Isis royalties in accordance with Section 5.9 on the Net Sales of such inventory of Licensed Products;

(b) each such Licensed Product will revert back to Isis as a Discontinued Product in accordance with Section 10.1 and Isis will have the obligation to pay royalties to GSK at a rate that is [***] percent ([***]%) of the otherwise applicable royalty under Section 5.10 with respect to such Discontinued Product;

(c) GSK will perform the obligations under Section 4.2.1 for the Collaboration Program to which such Discontinued Product relates, as though such obligations under Section 4.2 were obligations owed by GSK to Isis, *mutatis mutandis*; and

(d) except as explicitly set forth in this Section 9.3.2, Section 9.3.3, 9.3.4 or 9.3.5, GSK will have no further rights and Isis will have no further obligations with respect to the applicable terminated Collaboration Program(s).

The Parties acknowledge and agree that the special consequences set forth in this Section 9.3.2 constitute a genuine and reasonable good faith pre-estimate of the damages that will be suffered by Isis upon the occurrence of any termination by Isis pursuant to Section 9.2.2 or Section 9.2.3, or by GSK pursuant to Section 9.2.1, and will not be characterized as or deemed to be a penalty.

9.3.3. **Return of Information and Materials.** The Parties will return (or destroy, as directed by the other Party) all data, files, records and other materials containing or comprising the other Party's Confidential Information that are the subject of such termination. Notwithstanding the foregoing, the Parties will be permitted to retain one copy of such data, files, records, and other materials for archival purposes.

9.3.4. **Accrued Rights.** Termination of this Agreement (in whole or in part) for any reason will be without prejudice to any rights or financial compensation that will have accrued to the benefit of a Party prior to such termination or expiration, including, but not limited to, any obligation to reimburse Isis for research and/or Development expenses accrued under Section 1.7.1 or Section 1.7.2 prior to the date of such termination or expiration. Such termination or expiration will not relieve a Party from obligations that are expressly

indicated to survive the termination or expiration of this Agreement. For purposes of clarification, milestone payments under ARTICLE 5 accrue as of the date the applicable Milestone Event occurs even if the payment is not due under Section 5.8.2 until receipt of an invoice therefor.

9.3.5. **Survival.** The following provisions of this Agreement will survive the expiration or termination of the Agreement (in whole or in part): Section 3.2 (but only to the extent necessary to carry out the provisions of Section 9.3.1), Section 4.2.1 (but only to the extent necessary to satisfy the requirements of Section 9.3.1 or Section 9.3.2, as applicable), Section 4.4 (but only to the extent GSK is Developing or Commercializing a Licensed Compound or Licensed Product), Section 5.10, Section 5.12.3, Section 5.13, Section 5.14.2, Section 6.1.1, Section 6.1.2, Section 6.8, Section 7.5, Section 9.3, ARTICLE 6 (but only to the extent GSK is Developing or Commercializing a Licensed Compound or Licensed Product), ARTICLE 8, ARTICLE 10 (if the Agreement is terminated (i) by GSK under Section 9.2.1, or (ii) by Isis under Section 9.2.2 or Section 9.2.3), ARTICLE 11 and ARTICLE 12 and APPENDIX 1 (to the extent definitions are embodied in the foregoing listed Articles and Sections).

ARTICLE 10.
ISIS REVERSION RIGHTS

10.1. **Reversion Rights.** Isis may elect to continue to Develop and Commercialize any Discontinued Products that are the subject of a termination (i) by GSK under Section 9.2.1, or (ii) by Isis under Section 9.2.2 or Section 9.2.3, by notice in writing to GSK after such termination (an "***Election Notice***") that Isis is exercising its rights under this Section 10.1, in which case GSK will grant to Isis a sublicensable, worldwide, exclusive license or sublicense, as the case may be, to all GSK Technology Controlled by GSK as of the date of the Election Notice solely as they are necessary to make, have made, use, sell, offer for sale, have sold and import Discontinued Products. Such license will be sublicensable by Isis in accordance with Section 4.1.2, *mutatis mutandis*. In addition, if Isis provides GSK an Election Notice within ninety (90) days of such termination, then GSK will (x) assign back to Isis any GSK Orange Book Patents (or any other Patent Rights) that relate to such Discontinued Products assigned by Isis to GSK under this Agreement, and (y) transfer to Isis for Isis' use with respect to the Development and Commercialization of the Discontinued Products, any Know-How data, results, regulatory information, filings, and files in the possession of GSK as of the date of the Election Notice that relate to such Discontinued Products, and any other information or material specified in Section 4.2.1.

10.2. **Reversion Royalty Rates.** In consideration for the rights granted by GSK to Isis under Section 10.1, subject to the terms of this Agreement, Isis will pay a royalty on Net Sales of each Discontinued Product by Isis, its Affiliates and Sublicensees in accordance with Section 5.10 above.

ARTICLE 11.
CONFIDENTIALITY

11.1. **Confidentiality; Exceptions**. Except to the extent expressly authorized by this Agreement or otherwise agreed in writing, the Parties agree that, during the Agreement Term and for five (5) years thereafter, the receiving Party (the "***Receiving Party***") and its Affiliates will keep confidential and will not publish or otherwise disclose or use for any purpose other than as provided for in this Agreement any Know-How or other confidential and proprietary information and materials, patentable or otherwise, in any form (written, oral, photographic, electronic, magnetic, or otherwise) which is disclosed to it by the other Party (the "***Disclosing Party***") or its Affiliates or otherwise received or accessed by a Receiving Party in the course of performing its obligations or exercising its rights under this Agreement, including, but not limited to, trade secrets, Know-How, inventions or discoveries, proprietary information, formulae, processes, techniques and information relating to the past, present and future marketing, financial, and research and development activities of any product or potential product or useful technology of the Disclosing Party or its Affiliates and the pricing thereof (collectively, "***Confidential Information***"), except to the extent that it can be established by the Receiving Party that such Confidential Information:

11.1.1. was in the lawful knowledge and possession of the Receiving Party or its Affiliates prior to the time it was disclosed to, or learned by, the Receiving Party or its Affiliates, or was otherwise developed independently by the Receiving Party or its Affiliates, as evidenced by written records kept in the ordinary course of business, or other documentary proof of actual use by the Receiving Party or its Affiliates;

11.1.2. was generally available to the public or otherwise part of the public domain at the time of its disclosure to the Receiving Party or its Affiliates;

11.1.3. became generally available to the public or otherwise part of the public domain after its disclosure and other than through any act or omission of the Receiving Party or its Affiliates in breach of this Agreement; or

11.1.4. was disclosed to the Receiving Party or its Affiliates, other than under an obligation of confidentiality, by a Third Party who had no obligation to the Disclosing Party or its Affiliates not to disclose such information to others.

For clarity the fact that a particular Collaboration Target is included in a Collaboration Program is Confidential Information of GSK.

11.2. **Authorized Disclosure**. Except as expressly provided otherwise in this Agreement, a Receiving Party or its Affiliates may use and disclose to Third Parties Confidential Information of the Disclosing Party as follows: (i) with respect to any such disclosure of Confidential Information, under confidentiality provisions no less restrictive than those in this Agreement, and solely in connection with the performance of its obligations or exercise of rights granted or reserved in this Agreement (including, without limitation, the rights to Develop and Commercialize Compounds, Licensed Products, and/or Discontinued Products, and to grant licenses and sublicenses hereunder), *provided*, that Confidential Information may be disclosed by a Receiving Party to a governmental entity or agency without requiring such entity or agency to enter into a confidentiality agreement with such Receiving Party if such Receiving Party has used reasonable efforts to impose such requirement without success and disclosure to such governmental entity or agency is necessary for the performance of the Receiving Party's obligations hereunder; (ii) to the extent such disclosure is reasonably necessary in filing or prosecuting patent, copyright and

trademark applications (subject to Section 11.6 below), complying with applicable governmental regulations, obtaining Approvals, conducting Pre-Clinical Studies or Clinical Studies, marketing Licensed Products, or as otherwise required by applicable law, regulation, rule or legal process (including the rules of the SEC and any stock exchange); *provided, however*, that if a Receiving Party or any of its Affiliates is required by law or regulation to make any such disclosure of a Disclosing Party's Confidential Information it will, except where impracticable for necessary disclosures, for example, but without limitation, in the event of a medical emergency, give reasonable advance notice to the Disclosing Party of such disclosure requirement and will use its reasonable efforts to secure confidential treatment of such Confidential Information required to be disclosed; (iii) in communication with actual or potential lenders, investors, merger partners, acquirers, consultants, or professional advisors on a need-to-know basis, in each case under confidentiality provisions no less restrictive than those of this Agreement; (iv) to the extent and only to the extent that such disclosure is required to comply with existing expressly stated contractual obligations owed to such Party's or its Affiliates' licensor with respect to any intellectual property licensed to the other Party under this Agreement; or (v) to the extent mutually agreed to in writing by the Parties.

11.3. **Press Release; Disclosure of Agreement**. On or promptly after the Effective Date, the Parties will jointly issue a public announcement of the execution of this Agreement in form and substance substantially as set forth on SCHEDULE 11.3. Except to the extent required to comply with applicable law, regulation, rule or legal process or as otherwise permitted in accordance with this Section 11.3, neither Party nor such Party's Affiliates will make any public announcements, press releases or other public disclosures concerning this Agreement or the terms or the subject matter hereof without the prior written consent of the other, which will not be unreasonably withheld. Notwithstanding the foregoing, (a) except for scientific presentations and publications (which will be governed by Section 11.6 below) each Commercializing Party or its Affiliates may, without the other Party's approval, make disclosures pertaining solely to Licensed Products (as to GSK) or Discontinued Products (as to Isis), *provided, however*, that GSK will immediately notify (and provide as much advance notice as possible to) Isis of any event materially related to Licensed Products (including in such notice any disclosure of clinical data or results, material regulatory filings or Approval) so that the Parties may analyze the need for or desirability of publicly disclosing or reporting such event, any press release or other similar public communication by GSK related to efficacy or safety data and/or results of a Licensed Product will be submitted to Isis for review at least [***] ([***]) Business Days (to the extent permitted by law) in advance of such proposed public disclosure, Isis will have the right to expeditiously review and recommend changes to such communication and GSK will in good faith consider any changes that are timely recommended by Isis or GSK, as the case may be, and (b) to the extent information regarding this Agreement has already been publicly disclosed, either Party (or its Affiliates) may subsequently disclose the same information to the public without the consent of the other Party. Each Party will give the other Party a reasonable opportunity (to the extent consistent with law) to review all material filings with the SEC describing the terms of this Agreement prior to submission of such filings, and will give due consideration to any reasonable comments by the non-filing Party relating to such filing, including without limitation the provisions of this Agreement for which confidential treatment should be sought.

11.4. **Prior Confidentiality Agreement Superseded**. As of the Effective Date, this Agreement supersedes the Confidential Disclosure Agreement executed by Isis and GSK on September 26, 2008 (including any and all amendments thereto). All information exchanged between the Parties under that agreement will be deemed Confidential Information hereunder and will be subject to the terms of this ARTICLE 11.

11.5. **Remedies**. Notwithstanding Section 12.1, each Party will be entitled to seek, in addition to any other right or remedy it may have, at law or in equity, a temporary injunction, without the posting of any bond or other security, enjoining or restraining the other Party from any violation or threatened violation of this ARTICLE 11.

11.6. **Publications**.

(a) **Prior to Exercise of an Option**. Prior to GSK's exercise of an Option for a given Collaboration Program, all Compounds and Development Candidates with respect to such Collaboration Program will be considered the sole property of Isis, and Isis will be free, consistent with its practice with its other compounds and products, to publish and present data regarding any such Collaboration Program, and/or Development Candidate; *provided, however*, that GSK will have a right to review and comment on any such publications and Isis will incorporate GSK's requested changes unless there is a reasonable basis, that is discussed with GSK, to decline to do so. Notwithstanding the foregoing, Isis may not publish or present any data or information that contains any of GSK's Confidential Information without GSK's prior written consent.

(b) **After Exercise of an Option**. After GSK exercises its Option for a given Collaboration Program, GSK and Isis will publish and present data regarding any such Collaboration Program pursuant to the provisions of this Section 11.6(b). After GSK exercises its Option for a given Collaboration Program, and subject to this Section 11.6(b), GSK will have the right to publish summaries of results from any human clinical trials generated by Isis or GSK with respect to the Licensed Compounds without obtaining the consent of Isis and, except as required under Law, Isis may not publish any of such data, without the prior consent of GSK. The Parties will discuss and reasonably cooperate in order to facilitate the process to be employed in order to ensure the publication of any such summaries of human clinical trials data and results as required on the clinical trial registry of each respective Party, and will provide the other Party via submission to the Joint Patent Committee, at least [***] ([***]) days prior notice to review the clinical trials results to be published for the purposes of preparing any necessary Patent Rights filings. The Parties acknowledge that scientific lead time is a key element of the value of the Collaboration under this Agreement and further agree to use Commercially Reasonable Efforts to control public scientific disclosures of the results of the Development activities under this Agreement to prevent any potential adverse effect of any premature public disclosure of such results. The Parties will establish a procedure for publication review and each Party will first submit to the other Party through the Joint Patent Committee an early draft of all such publications, whether they are to be presented orally or in written form, at least [***] ([***]) days prior to submission for publication including, without limitation, to facilitate the publication of any summaries of human clinical trials data and

results as required on the clinical trial registry of each respective Party. Each Party will review such proposed publication in order to avoid the unauthorized disclosure of a Party's Confidential Information and to preserve the patentability of inventions arising from the Collaboration. If, as soon as reasonably possible, but no longer than [***] ([***]) days following receipt of an advance copy of a Party's proposed publication, the other Party informs such Party that its proposed publication contains Confidential Information of the other Party, then such Party will delete such Confidential Information from its proposed publication. In addition, if at any time during such [***] ([***]) day period, the other Party informs such Party that its proposed publication discloses inventions made by either Party in the course of the collaboration under this Agreement that have not yet been protected through the filing of a patent application, or the public disclosure of such proposed publication could be expected to have a material adverse effect on any Patents or Know-How solely owned or Controlled by such other Party, then such Party will either (a) delay such proposed publication, for up to [***] ([***]) days from the date the other Party informed such Party of its objection to the proposed publication, to permit the timely preparation and first filing of patent application(s) on the information involved or (b) remove the identified disclosures prior to publication.

11.7. **Acknowledgment**. Unless otherwise agreed upon in writing by the Parties, each Party will acknowledge in any press release, public presentation or publication regarding a Collaboration Program and/or a Licensed Product, the other Party's role in discovering and developing the Collaboration Program, Licensed Product and/or Discontinued Product, as applicable, and that such Collaboration Program, Licensed Products and Discontinued Products are under license from Isis and otherwise acknowledge the contributions from the other Party.

ARTICLE 12.
MISCELLANEOUS

12.1. **Dispute Resolution**.

12.1.1. **Escalation.** In the event any dispute, controversy or claim arises under, out of, in connection with or in relation to this Agreement, or the breach, termination, validity or enforceability of any provision hereof (a "***Dispute***"), the Parties will discuss and negotiate in good faith a solution acceptable to the Parties and in the spirit of this Agreement. If, after negotiating in good faith pursuant to the foregoing sentence the Parties fail to reach agreement within sixty (60) days, then the Dispute may be referred to the executives of each Party (the ***"Executives"***) for resolution at the request of either Party. If the Executives fail, after good-faith discussions, to reach an amicable agreement on the Dispute within ten (10) Business Days of submission to the Executives, then either Party's sole recourse is to submit such Dispute to binding arbitration pursuant to Section 12.1.2 after providing written notice to the other Party.

12.1.2. **Binding Arbitration.** Any controversy or claim arising out of or under this Agreement, or the breach thereof, which is not settled under the procedures set forth in the appropriate provisions of Section 1.3.3 or Section 12.1.1 and which is not subject to the final decision-making authority of a Party under the provisions of Section 1.3.3 will be finally resolved

by binding arbitration, held in New York City, New York, and administered by the American Arbitration Association under its Commercial Arbitration Rules. Judgment on the award rendered by the arbitrator(s) may be entered in any court having jurisdiction thereof. If the Parties cannot mutually agree on a single arbitrator, the Parties will make reasonable efforts to appoint three (3) arbitrators, who are each mutually acceptable to GSK and Isis, within forty-five (45) days of the initiation of the arbitration; in the event they are unsuccessful and do not agree to extend the time period, the arbitrators will be appointed in accordance with the rules. The Parties will share the expenses for the arbitrators, but will otherwise be responsible for their own fees in relation to such arbitration. Until such time as arbitrators are appointed, the Parties may seek judicial relief for interim measures, such as injunctive relief, in any court having competent jurisdiction. For clarity, the Parties understand and agree that binding arbitration pursuant to this Section 12.1.2 will not apply to alter or modify the indemnity obligations of the respective Parties under ARTICLE 8, but arbitration may be sought to interpret such obligations. For clarity, the Arbitrators will not have authority or discretion to decide any matter other than the matter for decision before them, and any such decision will not include any award or determination which would amend the applicable terms of this Agreement.

12.1.3. **Certain Matters Subject to Expert Panel.** If, at any time during the relevant Collaboration Term, the Parties cannot agree whether [***] has been demonstrated in a particular Collaboration Program, or whether any applicable Collaboration Target substituted in under Section 1.5.2 is primarily associated with a Rare Disease, the Parties will submit such matter to a panel of three (3) experts who are experienced in the field of biopharmaceuticals (an "***Expert Panel***"). All members of the Expert Panel must be mutually agreed by the Parties in good faith and as promptly as possible and must be free of any conflicts of interest with respect to either or both Parties. The Expert Panel will promptly hold a hearing to review the matter, at which they will consider briefs submitted by each Party at least fifteen (15) days before the hearing, as well as reasonable presentations that each Party may present. The Parties may elect to use separate Expert Panels for different Collaboration Programs in order to align the expertise of the members of the Expert Panels with the subject matter of the respective Collaboration Programs. The determination of the relevant Expert Panel as to such dispute will be binding on both Parties. The Parties will share equally in the costs of the Expert Panel, and each Party shall bear its own costs associated with preparing for and presenting to the Expert Panel. The Parties may also elect by mutual agreement to use an Expert Panel (or other panels of key opinion leaders) for guidance on other issues that may arise during the Collaboration Term.

12.2. **Governing Law.** This Agreement and any dispute arising from the performance or breach hereof will be governed by and construed and enforced in accordance with the laws of the State of Delaware, U.S.A., without reference to conflicts of laws principles.

12.3. **Assignment and Successors.** Neither this Agreement nor any obligation of a Party hereunder may be assigned by either Party without the consent of the other, which will not be unreasonably withheld, except that each Party may assign this Agreement and the rights, obligations and interests of such Party, in whole or in part, to any of its Affiliates, to any purchaser of all or substantially all of its assets or all or substantially all of its assets to which this Agreement relates or to any successor corporation resulting from any merger, consolidation, share exchange or other

similar transaction. In addition, Isis may assign or transfer its rights to receive royalties and milestones under this Agreement (but no liabilities and provided no security interest is granted to such Third Party in any Patent Rights that are licensed to GSK under this Agreement for a Licensed Product or Discontinued Product), without GSK's consent, to an Affiliate or to a Third Party in connection with a payment factoring transaction.

12.4. Change of Control.

12.4.1. In the event of a Change of Control of Isis, then, notwithstanding anything to the contrary in this Agreement, Isis will provide written notice to GSK of the closing of such Change of Control, and GSK will have the right, within [***] ([***]) days following the public announcement of the closing thereof, to either:

(a) exercise any unexercised Options by notifying Isis in writing of GSK's election to license any Collaboration Program at a pro-rata reduced Option exercise payment as compared to the Option exercise payment set forth in Section 5.4 ("***Reduced Option Payment***"), based upon the stage of Development of such Collaboration Program at the time of Change of Control as compared to completion of a Phase 2 PoC Trial stage of Development, which is set forth on SCHEDULE 12.4 hereto. Upon GSK's exercise of its option pursuant to this Section 12.4.1(a), GSK will be deemed to have obtained and Isis will be deemed to have granted the license set forth in Section 4.1.1 with respect to such Collaboration Program(s); or

(b) require Isis and its successor to reimburse GSK on a quarterly basis within [***] days of Isis' receipt of GSK's invoice, in an amount equal to the product of (i) the [***] *minus* the [***] *multiplied by* (ii) [***] percent ([***]%). The Parties will enter into any agreements required to address clinical safety, clinical trial responsibilities and regulatory matters to comply with applicable laws and regulations. In the event of GSK's exercise of its option pursuant to this Section 12.4.1(b) and the further completion of such Phase 2 PoC Trial, GSK will have the right to exercise its Option in accordance with this Agreement; or

(c) Allow such [***] ([***]) day period to lapse without providing any such notice of election under this Section 12.4.1, or otherwise provide Isis with written notice within such period electing not to exercise either of its options pursuant to Section 12.4.1(a) or Section 12.4.1(b) above, in either of which cases Isis and GSK will continue to perform and enjoy their respective rights and obligations with respect to such Collaboration Programs under the terms of this Agreement.

12.4.2. Upon GSK's exercise of its option pursuant to Section 12.4.1(a) or Section 12.4.1(b) above, Isis will carry out its technology transfer obligations pursuant to Section 4.2 with respect to such Collaboration Program(s). For the avoidance of doubt, except as set forth in this Section 12.4, all other terms and conditions of this Agreement will apply to any such license granted pursuant to GSK's exercise of its right hereunder.

12.4.3. Upon the occurrence of a Change of Control of Isis, Isis will no longer have any rights and GSK will no longer have any obligations under Section 4.3.3.

12.5. Performance Warranty. Each Party hereby acknowledges and agrees that it will be responsible for the full and timely performance as and when due under, and observance of all the covenants, terms, conditions and agreements set forth in, this Agreement by its Affiliates and Sublicensees.

12.6. Force Majeure. No Party will be held liable or responsible to the other Party nor be deemed to be in default under, or in breach of any provision of, this Agreement for failure or delay in fulfilling or performing any obligation of this Agreement when such failure or delay is due to force majeure, and without the fault or negligence of the Party so failing or delaying. For purposes of this Agreement, force majeure is defined as causes beyond the reasonable control of a Party, which may include, without limitation, acts of God; acts, regulations, or laws of any government; war; terrorism; civil commotion; destruction of production facilities or materials by fire, flood, earthquake, tornado, tsunami, explosion or storm; labor disturbances; pandemic; epidemic and failure of public utilities or common carriers. In such event the Party so failing or delaying will immediately notify the other Party of such inability and of the period for which such inability is expected to continue. The Party giving such notice will thereupon be excused from such of its obligations under this Agreement as it is thereby disabled from performing for so long as it is so disabled for up to a maximum of ninety (90) days, after which time the Parties will negotiate in good faith any modifications of the terms of this Agreement that may be necessary to arrive at an equitable solution, unless the Party giving such notice has set out a reasonable timeframe and plan to resolve the effects of such force majeure and executes such plan within such timeframe. To the extent possible, each Party will use reasonable efforts to minimize the duration of any force majeure.

12.7. Notices. Any notice or request required or permitted to be given under or in connection with this Agreement will be deemed to have been sufficiently given if in writing and personally delivered or sent by certified mail (return receipt requested), facsimile transmission (receipt verified), or overnight express courier service (signature required), prepaid, to the Party for which such notice is intended, at the address set forth for such Party below:

If to Isis, addressed to:

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008
Attention: Chief Operating Officer & CFO
Fax: 760-918-3592

with a copy to:

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008
Attention: General Counsel
Fax: 760-268-4922

If to GSK, addressed to:

Glaxo Group Limited

Glaxo Wellcome House, Berkeley Avenue,
Greenford. Middlesex
UB6 0NN, England
Facsimile: 44 20 8 047 6904
Attention: Company Secretary

with a copy to:

GlaxoSmithKline, LLC
2301 Renaissance Boulevard
Mail Code RN0220
King of Prussia, PA 19406
Attention: Vice President and
Associate General Counsel,
Legal Operations — Business Development
Fax: 610-787-7084

and a copy to:

Morgan, Lewis & Bockius LLP
502 Carnegie Center
Princeton, NJ 08540
Attention: Randall B. Sunberg
Fax: (609) 919-6701

or to such other address for such Party as it will have specified by like notice to the other Party; provided that notices of a change of address will be effective only upon receipt thereof. If delivered personally or by facsimile transmission, the date of delivery will be deemed to be the date on which such notice or request was given. If sent by overnight express courier service, the date of delivery will be deemed to be the next Business Day after such notice or request was deposited with such service. If sent by certified mail, the date of delivery will be deemed to be the third (3rd) Business Day after such notice or request was deposited with the U.S. Postal Service.

12.8. **Export Clause.** Each Party acknowledges that the laws and regulations of the United States restrict the export and re-export of commodities and technical data of United States origin. Each Party agrees that it will not export or re-export restricted commodities or the technical data of the other Party in any form without the appropriate United States and foreign government licenses.

12.9. **Waiver.** Neither Party may waive or release any of its rights or interests in this Agreement except in writing. The failure of either Party to assert a right hereunder or to insist upon compliance with any term or condition of this Agreement will not constitute a waiver of that right or excuse a similar subsequent failure to perform any such term or condition. No waiver by either Party of any condition or term in any one or more instances will be construed as a continuing waiver or subsequent waiver of such condition or term or of another condition or term.

12.10. **Severability.** If any provision hereof should be held invalid, illegal or unenforceable in any jurisdiction, the Parties will negotiate in good faith a valid, legal and enforceable substitute provision that most nearly reflects the original intent of the Parties and all other provisions hereof will remain in full force and effect in such jurisdiction and will be liberally construed in order to carry out the intentions of the Parties hereto as nearly as may be possible. Such invalidity, illegality or unenforceability will not affect the validity, legality or enforceability of such provision in any other jurisdiction.

12.11. **Entire Agreement.** This Agreement, together with the Schedules and Appendices hereto, sets forth all the covenants, promises, agreements, warranties, representations, conditions and understandings between the Parties and supersedes and terminates all prior agreements and

understanding between the Parties. There are no covenants, promises, agreements, warranties, representations, conditions or understandings, either oral or written, between the Parties other than as set forth herein and therein. No subsequent alteration, amendment, change or addition to this Agreement will be binding upon the Parties hereto unless reduced to writing and signed by the respective authorized officers of the Parties.

12.12. **Independent Contractors.** Nothing herein will be construed to create any relationship of employer and employee, agent and principal, partnership or joint venture between the Parties. Each Party is an independent contractor. Neither Party will assume, either directly or indirectly, any liability of or for the other Party. Neither Party will have the authority to bind or obligate the other Party and neither Party will represent that it has such authority.

12.13. **Headings.** Headings used herein are for convenience only and will not in any way affect the construction of or be taken into consideration in interpreting this Agreement.

12.14. **Books and Records.** Any books and records to be maintained under this Agreement by a Party or its Affiliates or Sublicensees will be maintained in accordance with U.S. Generally Accepted Accounting Principles (or any successor standard) in the case of Isis, and will be maintained in accordance with International Financial Reporting Standards in the case of GSK, consistently applied, except that the same need not be audited.

12.15. **Further Actions.** Each Party will execute, acknowledge and deliver such further instruments, and do all such other acts, as may be necessary or appropriate in order to carry out the expressly stated purposes and the clear intent of this Agreement.

12.16. **Construction of Agreement.** The terms and provisions of this Agreement represent the results of negotiations between the Parties and their representatives, each of which has been represented by counsel of its own choosing, and neither of which has acted under duress or compulsion, whether legal, economic or otherwise. Accordingly, the terms and provisions of this Agreement will be interpreted and construed in accordance with their usual and customary meanings, and each of the Parties hereto hereby waives the application in connection with the interpretation and

construction of this Agreement of any rule of law to the effect that ambiguous or conflicting terms or provisions contained in this Agreement will be interpreted or construed against the Party whose attorney prepared the executed draft or any earlier draft of this Agreement.

12.17. **Supremacy.** In the event of any express conflict or inconsistency between this Agreement and any Schedule or Appendix hereto, the terms of this Agreement will apply. The Parties understand and agree that the Schedules and Appendices hereto are not intended to be the final and complete embodiment of any terms or provisions of this Agreement, and are to be updated from time to time during the Agreement Term, as appropriate and in accordance with the provisions of this Agreement.

12.18. **Counterparts.** This Agreement may be signed in counterparts, each and every one of which will be deemed an original, notwithstanding variations in format or file designation which may result from the electronic transmission, storage and printing of copies of this Agreement from separate computers or printers. Facsimile signatures and signatures transmitted via PDF will be treated as original signatures.

12.19. **Compliance with Laws.** Each Party will, and will ensure that its Affiliates and Sublicensees will, comply with all relevant laws and regulations in exercising its rights and fulfilling its obligations under this Agreement.

[SIGNATURE PAGE FOLLOWS]

* - * - * - *

IN WITNESS WHEREOF, the Parties have caused this Agreement to be executed by their representatives thereunto duly authorized as of the Effective Date.

GLAXO GROUP LIMITED

By: */s/ Paul Williamson*
Name: Paul Williamson
Title: For and on behalf of Edinburgh Pharmaceutical Industries Limited
Corporate Director

ISIS PHARMACEUTICALS, INC.

By: */s/ B. Lynne Parshall*
Name: B. Lynne Parshall
Title: Chief Operating Officer and
Chief Financial Officer

List of Appendices and Schedules

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APPENDIX 1

DEFINITIONS

For purposes of this Agreement, the following capitalized terms will have the following meanings.

"***Acceptance***" means, with respect to an NDA filed for a Licensed Product, (a) in the United States, the receipt of written notice from the FDA in accordance with 21 C.F.R. § 314.101(a)(2) that such NDA is officially "*filed*," (b) in the European Union, receipt by GSK of written notice of acceptance by the EMEA of such NDA for filing under the centralized European procedure in accordance with any feedback received from European Regulatory Authorities; *provided that* if the centralized filing procedure is not used, then Acceptance will be determined upon the acceptance of such NDA by the applicable Regulatory Authority in a Major Country in the EU, and (c) in Japan, receipt by GSK of written notice of acceptance of filing of such JNDA from the Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto).

"***Affiliate***" of an entity means any corporation, firm, partnership or other entity, whether de jure or de facto, which directly or indirectly through one or more intermediaries controls, is controlled by or is under common control with a Party to this Agreement. An entity will be deemed to control another entity if it (i) owns, directly or indirectly, at least fifty percent (50%) of the outstanding voting securities or capital stock (or such lesser percentage which is the maximum allowed to be owned by a foreign corporation in a particular jurisdiction) of such other entity, or has other comparable ownership interest with respect to any entity other than a corporation; or (ii) has the power, whether pursuant to contract, ownership of securities or otherwise, to direct the management and policies of the entity. Notwithstanding the above, Regulus Therapeutics Inc. will not be deemed an "*Affiliate*" of Isis for the purposes of this Agreement under any circumstances.

"***Agreement***" will mean this Research, Development and License Agreement.

"***Agreement Term***" has the meaning set forth in Section 9.1.4.

"***Alliance Management Activities***" means the following:

(a) Promoting the overall health of the Collaboration and relationship between the Parties;

(b) Developing a mutually agreed alliance launch plan covering any activities and systems that the Parties need to implement within the first one hundred (100) days after the Effective Date to support the Collaboration;

(c) Organizing JSC meetings, including agendas, drafting minutes, and publishing final minutes;

(d) Creating and maintaining a current list of Collaboration Targets, Collaboration Programs (including whether such programs are Rare Disease Programs, CFB Programs or ID/Additional Programs), applicable Development Candidates and Back-Up Compounds, and Phase 2 PoC Trials, as determined pursuant to this Agreement;

(e) Supporting the co-chairs of the JSC with organization of meetings, information exchange, meeting minutes, and facilitating dispute resolution as necessary;

(f) Preparing status and progress reports on the above as determined necessary by the JSC;

(g) Ensuring compliance in maintaining Isis' Safety Database as outlined in Section 4.4; and

(h) Ensuring proper approval of publications prior to submission as required in Section 11.6.

"***Alliance Manager***" has the meaning set forth in Section 1.3.5.

"***Alnylam***" means Alnylam Pharmaceuticals, Inc.

"***Alnylam Agreement***" means that certain Amended and Restated Strategic Collaboration and License Agreement dated April 28, 2009 entered into between Isis and Alnylam.

[***][***]

"***ANDA***" means an Abbreviated New Drug Application and all amendments and supplements thereto filed with the FDA, or the equivalent application filed with any equivalent agency or governmental authority outside the U.S. (including any supra-national agency such as the EMEA in the EU).

"***Annual***" means a Calendar Year.

"***Antisense***" means the use of an ASO to modulate expression of a target gene.

"***API***" means the bulk active pharmaceutical ingredient manufactured in accordance with cGMP for a Development Candidate or Licensed Product.

"***Applicable Law***" or "***Law***" means all applicable laws, statutes, rules, regulations and other pronouncements having the effect of law of any federal, national, multinational, state, provincial, county, city or other political subdivision, agency or other body, domestic or foreign, including but not limited to any applicable rules, regulations, guidelines, or other requirements of the regulatory authorities that may be in effect from time to time.

"***Approval***" means, with respect to any Licensed Product in any regulatory jurisdiction, approval from the applicable Regulatory Authority sufficient for the manufacture, distribution, use and sale of the Licensed Product in such jurisdiction in accordance with Applicable Laws. In jurisdictions where the applicable Regulatory Authority sets the pricing authorizations necessary for a Licensed Product, except for MAA Approval, Approval will not be deemed to have occurred if the final approval to market and sell the Licensed Product is being withheld because GSK (or its Affiliates or Sublicensee) and the Regulatory Authority have not yet determined pricing even if all other approvals, licenses, registrations or authorizations necessary for marketing, sale and/or use of such Licensed Product in such jurisdiction have been obtained.

"***Aptamer***" means an oligonucleotide that was designed to specifically bind, and does specifically bind, to a target protein.

"***ASO***" means an oligonucleotide compound, or analog, mimic or mimetic thereof, having a sequence that is at least six (6) bases long and that modulates expression of a gene target via the binding, partially or wholly, of such compound to the RNA of such gene target.

"***Back-Up Compound***" means, with respect to a given Compound for a given Collaboration Program, any Compound other than the lead Development Candidate developed under such Collaboration Program, that (i) is identified at the time the lead Development Candidate is identified and has the same or similar chemistry as the lead Development Candidate and (ii) is designed to inhibit the same Collaboration Target as the lead Development Candidate. A "*Back-Up Compound*" includes, without limitation, any Development Candidate in a given Collaboration Program that has been modified, for example, by formulation, linker to antibody or any other targeting approach.

"***Bankruptcy Code***" has the meaning set forth in Section 9.2.5(b).

"***Base [***] Field***" has the meaning set forth in Section 1.6.2(b).

"***Base [***] Program***" has the meaning set forth in Section 1.6.2(b).

"***Breaching Party***" has the meaning set forth in Section 9.2.2(a).

"***Bring Down Date***" has the meaning set forth in Section 7.2.

"***Business Day***" means any day other than a Saturday or Sunday on which banking institutions in both New York, New York and London, England are open for business.

"***Calendar Quarter***" means a period of three (3) consecutive months ending on the last day of March, June, September, or December, respectively, and will also include the period beginning on the Effective Date and ending on the last day of the Calendar Quarter in which the Effective Date falls.

"***Calendar Year***" means a year of 365 days (or 366 days in a leap year) beginning on January 1 (or, with respect to 2009, the Effective Date) and ending on December 31, and so on year-by-year.

[***]

"***[***] Data Package***" has the meaning set forth in Section 1.6.2(c).

[***] means (i) the [***], so long as the [***] Program in the [***]remains the subject of a Collaboration Program or license granted under Section 4.1.1; and (ii) if GSK elects to pursue a [***] Program in the [***] (and pays Isis the applicable payments under [***]), the [***] will also include the [***] so long as the [***] remains the subject of a Collaboration Program or license granted under Section 4.1.1.

"***[***] Notice***" has the meaning set forth in Section 1.6.2(b).

"***[***] Program***" has the meaning set forth in Section 2.1.2(d).

"***[***] Program***" means a Collaboration Program focused on the gene target, [***] and will include (i) the Base [***] Program, (ii) the Same Compound-Expanded [***] Program if elected in accordance with Section 1.6.2, and (iii) the Different Compound-Expanded [***] Program if

elected in accordance with Section 1.6.2.

"***[***] Program***" has the meaning set forth in Section 2.1.2(d).

"***cGMP***" means current Good Manufacturing Practices as specified in the United States Code of Federal Regulations, ICH Guideline Q7A, or equivalent laws, rules, or regulations of an applicable Regulatory Authority at the time of manufacture.

"***Change of Control***" means, with respect to a Party, (a) a merger or consolidation of such Party with a Third Party which results in the voting securities of such Party outstanding immediately prior thereto ceasing to represent at least fifty percent (50%) of the combined voting power of the surviving entity immediately after such merger or consolidation, (b) a transaction or series of related transactions in which a Third Party, together with its Affiliates, becomes the owner of fifty percent (50%) or more of the combined voting power of the outstanding securities of such Party, (c) the sale or other transfer to a Third Party of all or substantially all of such Party's business to which the subject matter of this Agreement relates, (d) the stockholders or equity holders of such Party will approve a plan of complete liquidation of such Party or an agreement for the sale or disposition by such Party of all or a substantial portion of such Party's assets, other than pursuant to the transaction as described above or to an Affiliate, or (e) a change in the composition of the Board over a period of twelve (12) consecutive months or less such that a majority of the Board members ceases by reason of one or more contested elections by a Third Party for Board membership to be comprised of individuals whose election is not endorsed by a majority of the members of the Board immediately before the date of election.

"***Claims***" has the meaning set forth in Section 8.1.

"***Clinical Studies***" means human studies designed to measure the safety, efficacy, tolerability and/or appropriate dosage of a Compound, Licensed Compound or Licensed Product, as the context requires, including without limitation Phase 1 Trials, Phase 2 Trials (including any Phase 2 PoC Trial), Phase 3 Trials and any post-Approval studies (such as Phase 4 Trials).

"***Collaboration***" means the conduct of Collaboration Programs in accordance with this Agreement, including activities associated with any Back-Up Compounds and Follow-On Compounds in accordance with ARTICLE 1.

"***Collaboration Patents***" has the meaning set forth in Section 6.1.2.

"***Collaboration Program***" means (i) a research and development program set forth on APPENDIX 5 as of the Effective Date, (ii) the sixth (6^{th}) research and development program added to this Agreement in accordance with Section 1.5.1, and (iii) any research and development program substituted into this Agreement in accordance with Section 1.5.2.

"***Collaboration Program Research Plan***" has the meaning set forth in Section 1.4.1(c)(ii).

"***Collaboration Target***" means a gene target that is the subject of (i) a Collaboration Program set forth on APPENDIX 5 as of the Effective Date, (ii) the sixth (6^{th}) research and development program added to this Agreement in accordance with Section 1.5.1, or (iii) any research and development program substituted into this Agreement in accordance with Section 1.5.2.

"***Collaboration Target Acceptance Criteria***" has the meaning set forth in Section 1.5.1.

"***Collaboration Term***" has the meaning set forth in Section 1.2.

"***Combination Product***" will have the meaning assigned to such term in the definition of "*Net Sales*" below.

"***Commercialize***," "***Commercialization***" or "***Commercializing***" means any and all activities directed to marketing, promoting, detailing, distributing, importing, having imported, exporting, having exported, selling or offering to sell a Licensed Product following receipt of Approval for such Licensed Product in the applicable country, including, without limitation, conducting pre-and post-Approval activities, including studies reasonably required to increase the market potential of the Licensed Product and studies to provide improved formulation and Licensed Product delivery, and launching and promoting the Licensed Product in each Major Country.

"***Commercializing Party***" means (a) GSK, with respect to any Licensed Compounds and any Licensed Products other than Discontinued Products, in each case which are being Developed and Commercialized by or on behalf of GSK, its Affiliates or Sublicensees hereunder, and (b) Isis, with respect to any Discontinued Products, in each case which are being Developed and Commercialized by or on behalf of Isis, its Affiliates or Sublicensees hereunder.

"***Commercially Reasonable Efforts***" means the carrying out of discovery, research, development or commercialization activities using good-faith commercially reasonable and diligent efforts, using the efforts that the applicable Party would reasonably devote to a compound or product of similar market potential or profit potential at a similar stage in development or product life resulting from its own research efforts, based on conditions then prevailing and taking into account, without limitation, issues of safety and efficacy, regulatory authority-approved labeling, product profile, the competitiveness of alternative products in the marketplace, the likely timing of the product's entry into the market, the patent and other proprietary position, the likelihood of regulatory approval and other relevant scientific, technical and commercial factors.

"***Competitive Infringement***" has the meaning set forth in Section 6.5.1.

"***Compound***" means any ASO discovered by Isis that modulates the expression of a Collaboration Target via the binding, partially or wholly, of such ASO to the RNA of such Collaboration Target, and any salts, solvates, hydrates, hemihydrates, metabolites, enantiomers, racemates and all other optically active forms, prodrugs and conjugates of such ASO.

"***Confidential Information***" has the meaning set forth in Section 11.1.

"***Control***" or "***Controlled***" means, with respect to any patent or other intellectual property right, possession by a Party (including its Affiliates) of the right (whether by ownership, license or otherwise) to grant to the other Party access, ownership or a license, sublicense and/or other right to or under such patent or other intellectual property right as provided for herein without violating the terms of any agreement or other arrangement with any Third Party. Notwithstanding anything to the contrary under this Agreement, with respect to any Third Party that becomes an Affiliate of Isis after the Effective Date (as the result of a Change of Control wherein such Third Party acquires Isis), no intellectual property of such Third Party will be included in the licenses granted hereunder by virtue of such Third Party becoming an Affiliate of Isis, in each case where such intellectual property (1) existed at the time such Third Party became an Affiliate of Isis, or (2) is created by such Third Party after it becomes an Affiliate without using any Isis intellectual property.

"***Cover***," "***Covered***" or "***Covering***" means, with respect to a patent, that, but for rights granted to a Person under such patent, the practice by such Person of an invention claimed in such patent would infringe a Valid Claim included in such patent, or in the case of a patent that is a patent application, would infringe a Valid Claim in such patent application if it were to issue as a patent.

"***CREATE Act***" has the meaning set forth in Section 6.8.

"***Develop***," "***Developing***" or "***Development***" means with respect to a Compound or a Licensed Product, any and all discovery, characterization, or preclinical, clinical, or regulatory activity with respect to such Compound or Licensed Product to seek Approval (including the submission of all necessary filings with applicable Regulatory Authorities to support such preclinical and clinical activities and Approval), including human clinical trials conducted after Approval of such Licensed Product to seek Approval for additional Indications for such Licensed Product.

"Development Candidate" means any Compound targeting a Collaboration Target that is reasonably determined by Isis' RMC in accordance with Isis' standard procedures for designating development candidates as ready to start IND-Supporting Toxicology Studies except as otherwise set forth in APPENDIX 2(B) with respect to ID/Additional Programs. APPENDIX 2(A) lists examples of certain criteria Isis considers when determining whether a Compound should be designated a Development Candidate under the Rare Diseases Programs and the [***] Program. APPENDIX 2(B) lists examples of certain criteria Isis considers when determining whether a Compound should be designated a Development Candidate under the ID/Additional Programs.

"***Development Milestone Event***" has the meaning set forth in Section 5.5.1.

"***Different Compound-Expanded [***] Program***" has the meaning set forth in Section 1.6.2(d).

"***Disclosing Party***" has the meaning set forth in Section 11.1.

"***Discontinued Product***" means (x) a Returned Candidate, and/or (y) any Compound or Licensed Product that is the subject of a termination in the event GSK terminates this Agreement (or the applicable license under this Agreement) under Section 9.2.1 or Isis terminates this Agreement (or the applicable license under this Agreement) under Section 9.2.2 or 9.2.3.

"***Dispute***" has the meaning set forth in Section 12.1.1.

"***DMC***" means Isis' Development Management Committee, or any successor committee.

"***Effective Date***" has the meaning set forth in the Preamble of this Agreement.

"***Election Notice***" has the meaning set forth in Section 10.1.

"***EMEA***" means the European Medicines Agency and any successor entity thereto.

"***European Union***" or "***EU***" includes Austria, Belgium, Bulgaria, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, The Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, the United Kingdom, and any such other country or territory that may officially become part of the European Union after the Effective Date.

"***Estimated Incremental Costs***" has the meaning set forth in Section 1.6.2(d)(iii).

"***Executives***" has the meaning set forth in Section 12.1.1.

"***Expanded [***] Field***" has the meaning set forth in Section 1.6.2(b).

"***Expert Panel***" has the meaning set forth in Section 12.1.3.

"***First [***] Election Deadline***" has the meaning set forth in Section 1.6.2(b).

"***Final [***] Election Deadline***" has the meaning set forth in Section 1.6.2(c).

"***First Commercial Sale***" means the first sale of a Licensed Product by GSK, its Affiliate or a Sublicensee to a Third Party in a particular country after Approval of such Licensed Product has been obtained in such country.

"***Follow-On Compound***" means, with respect to a given Compound for a given Collaboration Program, any Compound other than the Development Candidate and Back-Up Compound developed under such Collaboration Program that is designed to inhibit the same Collaboration Target as such lead Development Candidate and Back-Up Compound but has a different chemistry. For clarity, a "*Follow-on Compound*" will not include any Back-Up Compound to the lead Development Candidate in a given Collaboration Program.

"***Generic Product***" means a Third Party's product(s) having the same or substantially the same active pharmaceutical ingredient as a Licensed Product and for which in the US an ANDA has been filed naming the Licensed Product as the reference listed drug or outside of the U.S., an equivalent process where bioequivalence to the Licensed Product has been asserted.

"***GLP***" means the then-current good laboratory practice standards promulgated or endorsed by the FDA as defined in 21 C.F.R. Part 58, and comparable foreign regulatory standards.

"***Good Data Management Practices***" has the meaning set forth in Section 1.4.6(a).

"***GSK***" has the meaning set forth in the Preamble of this Agreement.

"***GSK Collaboration Know-How***" has the meaning set forth in Section 6.1.2.

"***GSK Collaboration Patents***" has the meaning set forth in Section 6.1.2.

"***GSK Collaboration Technology***" has the meaning set forth in Section 6.1.2.

"***GSK Know-How***" means any Know-How Controlled by GSK on the Effective Date and/or during the Collaboration Term, *but specifically excluding* the GSK Collaboration Know-How.

"***GSK Know-How Royalty***" has the meaning set forth in Section 5.9.2(b).

"***GSK Orange Book Patents***" means the Patent Rights that are listed with, and/or are required to be listed with, applicable Regulatory Authorities Covering any Licensed Product being Developed by GSK, its Affiliates or Sublicensees hereunder that GSK, its Affiliate or Sublicensee intends to, or has begun to, Commercialize, and that have become the subject of an NDA submitted to any applicable Regulatory Authority, such listings to include, without limitation, all so-called "***Orange Book***" listings required under the Hatch-Waxman Act and all so-called "*Patent Register*" listings as required in Canada. For purposes of determining royalties payable under Section 5.9, GSK Orange Book Patents will include any and all foreign equivalent and counterpart Patent Rights to the Patent Rights described above.

"***GSK Patent***" means any Patent Rights included in the GSK Technology.

"***GSK Patent Royalty***" has the meaning set forth in Section 5.9.1.

"***GSK Product-Specific Patents***" means all Product-Specific Patents Controlled by GSK on or after the Effective Date.

"***GSK Supported Pass-Through Costs***" means (1) the licensing costs and payments payable by

Isis to Third Parties to the extent arising from Patent Rights, Know-How or other intellectual property rights that (i) are included in the Licensed Patents or Licensed Know-How; (ii) are necessary to Develop, Manufacture and/or Commercialize Compounds within a Collaboration Program, Licensed Compounds and/or Licensed Products; and (iii) [***]

"***GSK Technology***" means the GSK Collaboration Technology, Jointly-Owned Collaboration Technology, GSK Product-Specific Patents and any trademarks described in Section 4.1.5.

"***HSR***" means the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended.

[***]

"***ID/Additional Program***" means (i) the fifth (5th) Collaboration Program focused on [***]; and (ii) the sixth (6th), if any, Collaboration Program added to this Agreement in accordance with Section 1.5.1.

"***IDJSC***" has the meaning set forth in Section 1.3.6.

"***IND***" means an Investigational New Drug Application (as defined in the Food, Drug and Cosmetic Act, as amended) filed with the FDA or its foreign counterparts.

"***IND-Supporting Toxicology Studies***" means the pharmacokinetic and toxicology studies required to meet the requirements for filing an IND.

"***Indemnitee***" has the meaning set forth in Section 8.3.

"***Indication***" means, with respect to a Licensed Product, such Licensed Product's interference with a gene to affect a specific primary endpoint of a pathophysiologic state, regardless of etiology. For example only, in the disease of hypercholesterolemia, the reduction of LDL-C in different patient populations is considered the same Indication in each such population, irrespective of the fact that homozygous familial hypercholesterolemia (FH) patients, heterozygous FH patients, and severe hypercholesterolemia patients are distinct patient populations all having the same pathophysiologic state, as illustrated with examples set forth on APPENDIX 6 attached hereto. Conversely, and for example only, in the disease, age-related macular degeneration (AMD), the improvement of visual acuity in a patient population is considered a different Indication for patients with wet AMD as compared to patients with dry AMD, irrespective of the fact the drug treats the same endpoint (i.e., visual acuity), because wet AMD versus dry AMD are distinct pathophysiologic states.

"***Initiation of A Phase 1 Trial***" means the first visit by the first human subject in a Phase 1 Trial during which dosing of a Development Candidate occurs.

"***Initiation of A Phase 2 PoC Trial***" means the first visit by the first human subject in a Phase 2 PoC Trial during which dosing of a Development Candidate occurs.

"***Initiation of A Phase 3 Trial***" means the first visit by the first human subject in a Phase 3 Trial during which dosing of a Licensed Compound or Licensed Product occurs.

"***Integrated Product Plan***" or "***IPP***" has the meaning set forth in Section 4.3.3.

"***In Vivo Efficacy***" means, on an ID/Additional Program-by-ID/Additional Program basis, the Development Milestone Event that is achieved hereunder upon the later of (i) demonstration of pharmacodynamic modulation *in vivo* or, with respect to the fifth (5th) Collaboration Program, achievement of the criteria set forth on APPENDIX 7, in each case as confirmed by the JSC (subject to the dispute resolution provisions in Section 12.1.3, if the Parties cannot reach consensus), or (ii) designation of a Development Candidate for such ID/Additional Program.

"***Isis***" means Isis Pharmaceuticals, Inc.

"***Isis Collaboration Know-How***" has the meaning set forth in Section 6.1.2.

"***Isis Collaboration Patents***" has the meaning set forth in Section 6.1.2.

"***Isis Collaboration Technology***" has the meaning set forth in Section 6.1.2.

"***Isis Core Technology Patents***" means all Patent Rights Controlled by Isis or its Affiliates on or after the Effective Date necessary or useful for the Development and/or Commercialization of Licensed Compounds and/or Licensed Products, in any case other than Isis Product-Specific Patents or Isis Manufacturing and Analytical Patents. A list of Isis Core Technology Patents as of the Effective Date is set forth on SCHEDULE 7.2.5(a) attached hereto.

"***Isis Database***" has the meaning set forth in Section 4.4.1.

"***Isis Follow-On Product***" has the meaning set forth in Section 2.1.2(c).

"***Isis In-License Agreements***" has the meaning set forth in Section 5.11.1(a).

"***Isis Know-How***" means any Know-How Controlled by Isis or its Affiliates on or after the Effective Date, including any Jointly-Owned Collaboration Know-How and Isis Collaboration Know-How, necessary or useful for the Development and/or Commercialization of Licensed Compounds and/or Licensed Products. Isis Know-How does not include the Isis Manufacturing and Analytical Know-How.

"***Isis Manufacturing and Analytical Know-How***" means Know-How Controlled by Isis or its Affiliates on or after the Effective Date, including Jointly-Owned Collaboration Know-How that relates to the synthesis or analysis of Licensed Compounds and/or Licensed Products regardless of sequence or chemical modification. Isis Manufacturing and Analytical Know-How does not include the Isis Know-How.

"***Isis Manufacturing and Analytical Patents***" means Patent Rights Controlled by Isis or its Affiliates on or after the Effective Date, including Jointly-Owned Collaboration Patents, that claim methods and materials used in the synthesis or analysis of Licensed Compounds and/or Licensed Products regardless of sequence or chemical modification. A list of Isis Manufacturing and Analytical Patents as of the Effective Date is set forth on SCHEDULE 7.2.5(b) attached hereto. Isis Manufacturing and Analytical Patents do not include the Product-Specific Patents or the Isis Core Technology Patents.

"***Isis Orange Book Patents***" means the Patent Rights that are listed with, and/or are required to be listed with, applicable Regulatory Authorities Covering any Discontinued Product being Developed by Isis, its Affiliates or Sublicensees hereunder, that Isis, its Affiliate or Sublicensees intend to, or has begun to, Commercialize, and that have become the subject of an NDA submitted to any applicable Regulatory Authority, such listings to include, without limitation, all so-called "***Orange Book***" listings required under the Hatch-Waxman Act and all so-called "***Patent Register***" listings as required in Canada. For purposes of determining royalties payable under Section 5.10, Isis Orange Book Patents will include any and all foreign equivalent and counterpart Patent Rights to the Patent Rights described above.

"***Isis Patents***" means any Patent Rights included in the Licensed Patents.

"***Isis Product-Specific Patents***" means all Product-Specific Patents Controlled by Isis or its Affiliates on or after the Effective Date necessary or useful for the Development and/or Commercialization of Licensed Compounds and/or Licensed Products. A list of Isis Product-Specific Patents as of the Effective Date is set forth on SCHEDULE 7.2.5(c) attached hereto. For purposes of clarification, any Isis Product-Specific Patents assigned to GSK as set forth in Section 6.2.2(b) will still be considered Isis Product-Specific Patents for determining the royalty term and applicable royalty rates under ARTICLE 5.

"***Isis Supported Pass-Through Costs***" means (1) the licensing costs and payments payable by Isis to Third Parties to the extent arising from any Third Party intellectual property in-licensed by Isis that is (i) included in the Licensed Patents or Licensed Know-How; and (ii) necessary to Develop, Manufacture and/or Commercialize Compounds within a Collaboration Program, Licensed Compounds and/or Licensed Products; and (2) all costs and payments of any kind owing to [***] or its affiliate under that certain [***]; *provided*, *however*, that "*Isis Supported Pass-Through Costs*" specifically excludes any licensing costs and payments owed to a Third Party that primarily claim or Cover [***].

"***Japan NDA***" or "***JNDA***" means the Japanese equivalent of an NDA filed with the Koseisho (*i.e.*, the Japanese Ministry of Health and Welfare, or any successor agency thereto).

"***JNDA Approval***" means the Approval of a JNDA by the Koseisho (*i.e.*, the Japanese Ministry of Health and Welfare, or any successor agency thereto) for the applicable Licensed Product in Japan.

"***JNDA Filing***" means the acceptance by the Koseisho (*i.e.*, the Japanese Ministry of Health and Welfare, or any successor agency thereto) of the filing of a JNDA for the applicable Licensed Product.

"***Joint Patent Committee***" will have the meaning set forth in Section 6.1.3.

"***Jointly-Owned Collaboration Know-How***" has the meaning set forth in Section 6.1.2.

"***Jointly-Owned Collaboration Patents***" has the meaning set forth in Section 6.1.2.

"***Jointly-Owned Collaboration Technology***" has the meaning set forth in Section 6.1.2.

"***JSC***" has the meaning set forth in Section 1.3.1.

"***Know-How***" means inventions, technical information, know-how and materials, including technology, software, instrumentation, devices, data, compositions, formulas, biological materials, assays, reagents, constructs, compounds, discoveries, procedures, processes, practices, protocols, methods, techniques, results of experimentation or testing, knowledge, trade secrets, skill and experience, in each case whether or not patentable or copyrightable.

"***Licensed Compound***" means any Compound included in a Collaboration Program for which GSK has exercised its Option under Section 3.1 of this Agreement.

"***Licensed IP***" means the Licensed Patents and Licensed Know-How.

"***Licensed Know-How***" means Isis Manufacturing and Analytical Know-How, and Isis Know-How.

"***Licensed Patents***" means the Isis Product-Specific Patents, Isis Core Technology Patents and Isis Manufacturing and Analytical Patents.

"***Licensed Product***" means a pharmaceutical product having a Licensed Compound as its active ingredient.

"***Losses***" has the meaning set forth in Section 8.1.

"***MAA Approval***" means the receipt of the first Approval for the applicable Licensed Product in any EU country, and the grant of pricing and reimbursement approval for such Licensed Product at a level acceptable to GSK [***].

"***MAA Filing***" means filing with the EMEA of a marketing authorization application ("***MAA***") for the applicable Licensed Product under the centralized European procedure. If the centralized EMEA filing procedure is not used, MAA Filing will be achieved upon the first filing of an MAA for the applicable Licensed Product in any Major Country.

"***Major Country***" will mean any of the following countries: the United States, Japan, the United Kingdom, Germany, France, Italy or Spain and, [***].

"***Major EU Markets***" means the United Kingdom, France, Germany, Italy and Spain.

"***Manufacture***" or "***Manufacturing***" means any activity involved in or relating to the manufacturing, quality control testing (including in-process, release and stability testing), releasing or packaging, for pre-clinical and clinical purposes, of API, a Compound, or a Licensed Product.

"***Milestone Event***" means a Development Milestone Event or a Sales Milestone Event, as the case may be.

"***NDA***" means a New Drug Application filed with the FDA after completion of clinical trials to obtain Approval for the applicable Licensed Product in the United States.

"***NDA Approval***" means the Approval of an NDA by the FDA for the applicable Licensed Product in the U.S.

"***NDA Filing***" means the acceptance by the FDA of the filing of an NDA for the applicable Licensed Product.

"***Net Sales***" means, with respect to any Licensed Product, the gross invoiced sales of such Licensed Product sold by either (i) GSK, its Affiliates or Sublicensees or (ii) as the case requires, Isis, its Affiliates or Sublicensees (in each case, the "***Selling Party***"), in finished product form, packaged and labeled for sale, under this Agreement in arm's-length sales to Third Parties, less the following deductions which are actually incurred, allowed, paid, accrued or specifically allocated to the Third Party customer by the Selling Party (to the extent actually taken by such Third Party customer), on such sales for: (a) customary trade, quantity, and cash discounts; (b) customary and reasonable credits, rebates and chargebacks (including those to managed-care entities and government agencies including Medicare and Medicaid), and allowances or credits to customers on account of rejection or returns (including, but not limited to, wholesaler and retailer returns) or on account of retroactive price reductions affecting such Licensed Product; (c) freight, postage and duties, and transportation charges relating to such Licensed Product, including handling and insurance thereto; (d) sales taxes, value added taxes (VAT), and other taxes directly linked to the sales of such Licensed Product to the extent included in the gross amount invoiced; (e) actual bad debt, in an amount up to 2% of Net Sales; (f) commissions

allowed or paid to Third Party distributors, brokers, or agents relating to such Licensed Product other than sales personnel, sales representatives, and sales agents employed by the Selling Party; and (g) any other items actually deducted from gross invoiced sales amounts as reported by such Party in its financial statements in accordance with, in the case of GSK's Net Sales, the International Financial Reporting Standards, applied on a consistent basis, and, in the case of Isis' Net Sales, the U.S. generally accepted accounting principles applied on a consistent basis.

Net Sales will not include any transfer or sale between or among a Party and any of its Affiliates or direct Sublicensees unless as part of a commercial sale and the paying party is the end user of the relevant Licensed Product.

A Licensed Product provided to patients free of charge for compassionate use will not be included in Net Sales.

In the event a Licensed Product is sold as part of a Combination Product (as defined below), the Net Sales from the Licensed Product, for the purposes of determining royalty payments, will be determined by multiplying the Net Sales (as determined without reference to this paragraph) of the Combination Product by the fraction A/A+B, where A is the average net sales price (determined substantially in accordance with the above) of the Licensed Product when sold separately in finished form and B is the average net sales price (determined substantially in accordance with the above) of the other therapeutically active pharmaceutical compound(s) included in the Combination Product when sold separately in finished form, each during the applicable royalty period or, if sales of all compounds did not occur in such period, then in the most recent royalty reporting period in which sales of all occurred. In the event that such average net sales price cannot be determined for both the Licensed Product and all other therapeutically active pharmaceutical compounds included in the Combination Product, Net Sales for the purposes of determining royalty payments will be calculated as above, but the average net sales price in the above equation will be replaced by a good-faith estimate of the fair market value of the compound(s) for which no such price exists. As used above, the term "***Combination Product***" means any pharmaceutical product which consists of a Licensed Product and any other therapeutically active pharmaceutical compound(s).

"***Non-Breaching Party***" has the meaning set forth in Section 9.2.2(a).

"***Objective***" has the meaning set forth in Section 1.1.

[***]

"***Option***" means GSK's exclusive option set forth in Section 3.1 to exclusively license a Collaboration Program.

"***Option Deadline***" has the meaning set forth in Section 3.1.

"***Option Exercise Effective Date***" has the meaning set forth in Section 3.2.3.

"***Party***" or "***Parties***" means GSK and Isis individually or collectively.

"***Patent Costs***" will mean the reasonable fees and expenses paid to outside legal counsel, and filing, maintenance and other reasonable out-of-pocket expenses paid to Third Parties, incurred in connection with the Prosecution and Maintenance of Patent Rights.

"***Patent Rights***" means (a) patents, patent applications and similar government-issued rights protecting inventions in any country or jurisdiction however denominated, (b) all priority applications, divisionals, continuations, substitutions, continuations-in-part of and similar applications claiming priority to any of the foregoing, and (c) all patents and similar government-issued rights protecting inventions issuing on any of the foregoing applications, together with all registrations, reissues, renewals, re-examinations, confirmations, supplementary protection certificates, and extensions of any of (a), (b) or (c).

"***Permitted Licenses***" means (1) licenses granted by Isis before and after the Effective Date to any Third Party under the Isis Core Technology Patents, the Isis Manufacturing and Analytical Patents, or the Isis Manufacturing and Analytical Know-How (but not under the Isis Product-Specific Patents) to (a) use oligonucleotides (or supply oligonucleotides to end users) in quantities not to exceed [***] per oligonucleotide per end user solely to conduct Pre-Clinical Research, or (b) enable such Third Party to broadly manufacture or formulate oligonucleotides, where such Third Party is primarily engaged in providing contract manufacturing or services and is not engaged in drug discovery, development or commercialization; and (2) material transfer agreement with academic collaborators or non-profit institutions to conduct noncommercial research on gene targets.

"***Person***" will mean any corporation, limited or general partnership, limited liability company, joint venture, trust, unincorporated association, governmental body, authority, bureau or agency, any other entity or body, or an individual.

"***Phase 1 Trial***" means a Clinical Study in any country, the principle purpose of which is a preliminary determination of safety in healthy individuals or patients that would satisfy the requirements of 21 CFR 312.2(a), or an equivalent clinical study required by a Regulatory Authority in a jurisdiction outside of the United States.

"***Phase 1 Trial Design/Endpoints for an ID/Additional Program***" means the clinical trial design and primary/secondary endpoints for an ID/Additional Program (i) to be discussed in consultation with the IDJSC and subject to GSK's decision making authority, mutually agreed by Isis and GSK at such time, if at all, as a Development Candidate is ready to initiate a Phase 1 Trial and (ii) intended by GSK to meet both sets of the Phase 1 Success Criteria set forth in APPENDIX 8(B).

"***Phase 2 PoC Data Package***" means, with respect to a particular Development Candidate, [***]

"***Phase 2 PoC Trial***" means, with respect to a Collaboration Program, the first phase 2a Clinical Study(ies) in human patients designed to provide evidence of short-term safety, efficacy and tolerability of a Development Candidate within such Collaboration Program. For clarity, for an ID/Additional Program, the first Clinical Study in HBV infected patients shall not be deemed a Phase 2 PoC Trial, unless otherwise mutually agreed in writing by GSK and Isis.

"***Phase 2 PoC Trial Costs***" means internal and/or external expenses and costs of a Phase 2 PoC Trial, including, without limitation, investigator grants, laboratory services, clinical PK assays, carcinogenicity studies, CMC studies, CRO services and pass-throughs, pharmacovigilance and risk management activities, costs for packaging, distribution and reconciliation (including labels and translations, inventory control, IVRS, off-site storage and destruction),

data management (including EDC), clinical study reports, drug costs (API, Compound or drug product containing a Compound) at Isis' Cost of Goods, investigator meetings, monitoring, DSMB costs, program-specific travel, metabolomics assays, courier services, clinical trial liability insurance costs (allocated to such trial) quality assurance costs for auditing clinical trial activities and preclinical

studies support (report reviews and CMC review). Isis' internal costs with respect to its employees performing such activities will be calculated at the FTE Rate at such time.

(a) "***Cost of Goods***" means, with respect to units of Compound or drug product containing such Compound manufactured by or on behalf of Isis, the fully absorbed cost incurred by Isis to manufacture such Compound and such drug product as calculated and determined in good faith by Isis using the procedures and methodologies described in APPENDIX 4 which are used by Isis to calculate and determine the cost incurred by Isis to manufacture compounds and products for Isis' Third Party collaboration partners.

(b) "***FTE***" means the equivalent of the work of one (1) employee with appropriate professional scientific and/or technical or managerial experience, working on a dedicated full-time basis for one (1) year (consisting of at least a total of one thousand eight hundred twenty (1,820) hours per year of dedicated effort, excluding vacations and holidays) of work. Overtime will not be counted toward the number of hours that are used to calculate the FTE contribution.

(c) "***FTE Rate***" means the fully burdened rate Isis charges its Third Party collaboration partners for Isis FTEs.

"***Phase 2 Trial***" means a Clinical Study conducted in any country that is intended to explore a variety of doses, dose response and duration of effect to generate initial evidence of clinical safety and activity in a target patient population, that would satisfy the requirements of 21 CFR 312.21(b), or an equivalent Clinical Study required by a Regulatory Authority in a jurisdiction outside of the United States. A "*Phase 2 Trial*" includes a Phase 2 PoC Trial.

"***Phase 3 Trial***" means a pivotal Clinical Study (whether or not denominated as a "*Phase 3*" Clinical Study under applicable regulations) in human patients that is of the size and design agreed to by a Regulatory Authority to be appropriate to establish that the Licensed Product is safe and effective for its intended use; to define warnings, precautions and adverse reactions that are associated with the Licensed Product in the dosage range to be prescribed; and to support Approval of such Licensed Product.

"***Phase 4 Trial***" means a Clinical Study in any country which is conducted after Approval of a Licensed Product has been obtained from an appropriate Regulatory Authority, consisting of trials conducted voluntarily for enhancing marketing or scientific knowledge of an approved Indication and trials conducted due to request or requirement of a Regulatory Authority.

"***Platform Blocking IP***" means Third Party intellectual property that is necessary to Develop and/or Commercialize a particular Licensed Product, where the financial obligations for which would have been considered Isis Supported Pass-Through Costs had Isis Controlled such Platform Blocking IP on the Effective Date.

"***PoC Cost Limit***" has the meaning set forth in Section 1.7.1.

"***PoC Success Criteria***" means the criteria to be discussed and, subject to [***] promptly mutually agreed by Isis and GSK at such time, if at all, as a Collaboration Program reaches the Development Candidate stage (as may be further refined through consultations with the JSC). APPENDIX 8(A) lists PoC Success Criteria for the Rare Diseases Programs and the [***] Program and APPENDIX 8(B) lists Phase 1 Success Criteria and PoC Success Criteria for ID/Additional Program.

"***PoC Trial Completion Notice***" has the meaning set forth in Section 3.1.

"***PoC Trial Design/Endpoints***" means the clinical trial design and primary/secondary endpoints (i) to be discussed in consultation with the JSC and subject to [***], mutually agreed by Isis and GSK at such time, if at all, as a Development Candidate is ready to initiate a Phase 2 PoC Trial and (ii) intended by GSK to meet the PoC Success Criteria.

"***Pre-Clinical Research***" means pre-clinical research including gene function, gene expression and target validation research using cells and animals, which may include small pilot toxicology studies *but excludes* pharmacokinetic and toxicology studies required to meet the regulations for filing an IND, Development and Commercialization.

"***Pre-Clinical Studies***" means *in vitro* and *in vivo* studies of a Compound, not in humans, including those studies conducted in whole animals and other test systems, designed to determine the toxicity, bioavailability, and pharmacokinetics of a Compound and whether the Compound has a desired effect.

"***Prior Agreements***" means the agreements listed on SCHEDULE 7.2.7 attached hereto.

"***Proceeding***" means an action, suit or proceeding.

"***Product-Specific Patents***" means Patents Controlled by a Party or any of its Affiliates on or after the Effective Date, including any Collaboration Patents, claiming (i) the specific composition of matter of a Licensed Compound and/or a Licensed Product, or (ii) methods of using a Licensed Compound and/or a Licensed Product as a therapeutic; *provided however*, patents Controlled by Isis or any of its Affiliates that (x) include claims that are directed to subject matter applicable to ASOs in general, or (y) include an ASO, the sequence of which targets a Collaboration Target and a gene target that is not a Collaboration Target, will not be considered Product-Specific Patents, and in the case of (x) and (y), such patents will be considered Isis Core Technology Patents.

"***Product Development Plan***" has the meaning set forth in Section 4.3.3.

"***Prosecution and Maintenance***" or "***Prosecute and Maintain***" means, with regard to a Patent Right, the preparing, filing, prosecuting and maintenance of such Patent Right, as well as handling re-examinations, reissues, and requests for patent term extensions with respect to such Patent Right, together with the conduct of interferences, the defense of oppositions and other similar proceedings with respect to the particular Patent. For clarification, "***Prosecution and Maintenance***" or "***Prosecute and Maintain***" will not include any other enforcement actions taken with respect to a Patent Right.

"***Rare Disease***" means (i) a disease or condition for which the intended drug affects fewer than 200,000 people in the United States or, if the drug is a vaccine, diagnostic drug, or preventive drug, the persons to whom the drug will be administered in the United States are fewer than 200,000 per year as specified in Sec. 316.21(b) of the Federal Food, Drug and Cosmetic Act (the "***Act***"), or (ii) a diseases or conditions affecting 200,000 or more people, or for a vaccine,

diagnostic drug, or preventive drug to be administered to 200,000 or more persons per year in the United States, there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the United States as specified in Sec. 316.21(c) of the Act.

"***Rare Disease Program***" means the respective Collaboration Programs focused on each of the Collaboration Targets, [***], or the [***] or any replacement target for such targets as determined in accordance with Section 1.5.2, which replacement target may or may not be primarily associated with a Rare Disease.

"***Receiving Party***" has the meaning set forth in Section 11.1.

"***Reduced Option Payment***" has the meaning set forth in Section 12.4.

"***Regulatory Authority***" means any governmental authority, including the FDA, EMEA or Koseisho (*i.e.*, the Japanese Ministry of Health and Welfare, or any successor agency thereto), that has responsibility for granting any licenses or approvals or granting pricing and/or reimbursement approvals necessary for the marketing and sale of a Licensed Product in any country.

"***Returned Candidate***" means any Development Candidate for which GSK's exclusive Option under Section 3.1 has expired.

"***Reverse Royalties***" has the meaning set forth in Section 5.10.1.

[***]

[***]

"***[***] Election Deadline***" has the meaning set forth in Section 1.6.1.

"***[***] Sanction Notice"*** has the meaning set forth in Section 1.6.1.

"***RMC***" means Isis' Research Management Committee, or any successor committee.

"***Sales Milestone Event***" has the meaning set forth in Section 5.7.

"***Same Compound-Expanded [***] Program***" has the meaning set forth in Section 1.6.2(c).

"***Sanctioned Target***" means a Collaboration Target with respect to which therapeutic potential has been demonstrated in pre-clinical disease models and such Collaboration Target has received approval by Isis' RMC to expend resources to identify a human Development Candidate, all in accordance with Isis' standard processes. APPENDIX 3 lists examples of certain criteria Isis considers when determining whether a gene target should be approved as a Sanctioned Target. As of the Effective Date, [***] are each Sanctioned Targets.

"***Significant Sequence Homology***" means, with respect to an ASO Isis is practicing and the Compound being Developed or Commercialized under the CFB Program, the ASO comprises [***] or more identical, contiguous nucleobases of such Compound sequence. For example only, an ASO with a sequence comprising [***] or more identical, contiguous nucleobases of a Compound having a sequence that is [***] nucleobases in length has Significant Sequence Homology. Conversely, an ASO with a sequence comprising [***] or less identical, contiguous nucleobases of such Compound having a sequence that is [***] nucleobases in length does not have Significant Sequence Homology.

"***Sublicensee***" means a Third Party to whom a Party or its Affiliates or Sublicensees has granted a sublicense or license under any Licensed IP or GSK Technology, as the case may be, licensed to such Party in accordance with the terms of this Agreement.

[***]

"***Termination Payment***" has the meaning set forth in Section 9.2.1.

"***Third Party***" means a Person or entity other than the Parties or their respective Affiliates.

"***Third Party Obligations***" means any financial and non-financial encumbrances, restrictions, or limitations imposed by an agreement between Isis and a Third Party that relate to a Compound, Licensed Product and/or a Collaboration Target, including, without limitation, field or territory restrictions, covenants, milestone payments, diligence obligations, sublicense revenue, royalties, or other payments.

[***]

"***UK Tax Certification"*** has the meaning set forth in Section 5.14.2.

"***United States***" or "***U.S.***" means the fifty states of the United States of America and all of its territories and possessions and the District of Columbia.

"***Unvalidated Collaboration Program***" has the meaning set forth in Section 1.5.2.

"***Valid Claim***" means a claim of any issued or unexpired patent that has not been revoked or held unenforceable or invalid by a decision of a court or governmental agency of competent jurisdiction from which no appeal can be taken, or with respect to which an appeal is not taken within the time allowed for appeal and that has not been disclaimed or admitted to be invalid or unenforceable through reissue, disclaimer or otherwise.

"***Voluntarily Terminated Collaboration Program***" has the meaning set forth in Section 9.2.1.

APPENDIX 2(A)

Isis' Development Candidate Designation Criteria for Rare Disease Programs / [***] Programs

[***]

APPENDIX 2(B)

Isis' Development Candidate Designation Criteria for ID/Additional Programs

Milestone: Candidate Selection Criteria

[***]

Appendix 3

Target Sanction Checklist

[***]

APPENDIX 4

2010 Estimate of API Cost per Kilogram
(000's)

[***]

APPENDIX 5

Collaboration Programs and Collaboration Targets

	Collaboration Target	Collaboration Program
1	[***]	[***]
2	[***]	[***]
3	[***]	[***]
4	[***]	[***]
5	[***]	[***]

APPENDIX 6

Examples Illustrating Indications

Primary endpoint(s)	pathophysiologic state, disease, human condition regardless of etiology
weight loss	obesity
LDL, Total Cholesterol	Hypercholesterolemia
HbA1c	Type 2 diabetes
breast tumor size	breast cancer
airway restriction	asthma

APPENDIX 7

[***] Criteria for ID/Additional Program for [***]

[***]

APPENDIX 8(A)

PoC Success Criteria for Rare Disease Programs / [***] Programs

[***]

APPENDIX 8(B)

Phase I Success Criteria and PoC Success Criteria for ID/Additional Programs

[***]

SCHEDULE 2.1.2(c)

ROFN Terms

If Isis (a) has a good-faith desire to offer a Third Party an exclusive license to such Isis Follow-On Product, or (b) Initiates a Phase 3 Trial for such Isis Follow-On Product, then Isis will promptly (but in any case within thirty (30) days) provide written notice to GSK, and Isis will promptly deliver to GSK evaluation materials reasonably relevant to such Isis Follow-On Product and no less than those materials provided to applicable Third Parties, including information consistent with the information Isis is required to disclose as part of a Phase 2 PoC Data Package. GSK will then have forty-five (45) days to notify Isis in writing whether GSK desires to exclusively license such Isis Follow-On Product. If GSK provides Isis with timely written notice that GSK desires to exclusively license such Isis Follow-On Product, then Isis and GSK will, in good faith, use commercially reasonable efforts to conclude a written license agreement within one hundred twenty (120) days. If GSK fails to timely notify Isis that GSK desires to exclusively license such Isis Follow-On Product, or if despite good faith commercially reasonable efforts GSK and Isis are unable to reach an agreement within one hundred twenty (120) days after Isis' receipt of such notice from GSK, then Isis may grant an exclusive license to any Third Party to such Isis Follow-On Product on economic terms which, when taken as a whole, are no more favorable to any such Third Party than the terms last offered under this right of first negotiation by GSK to Isis.

SCHEDULE 5.11.1

ISIS IN-LICENSE AGREEMENTS
(RELEVANT TO COLLABORATION PROGRAMS AS OF THE EFFECTIVE DATE)

[***]

SCHEDULE 7.2.5(a)

ISIS CORE TECHNOLOGY PATENTS

[***]

SCHEDULE 7.2.5(b)

Isis Manufacturing and Analytical Patents

[***]

SCHEDULE 7.2.5(c)

Isis Product-Specific Patents

[***]

SCHEDULE 7.2.7

PRIOR AGREEMENTS

[***]

****

AGREEMENTS CREATING THIRD PARTY OBLIGATIONS
(AS OF THE EFFECTIVE DATE)

[***]

Schedule 11.3

GSK and Isis Pharmaceuticals collaborate on RNA therapeutics for rare and infectious diseases

- **GSK has right to license and commercialize compounds at clinical proof-of-concept**
- **Isis gives GSK access to expertise in discovery and development of anti-RNA therapeutics**

LONDON, United Kingdom, and CARLSBAD, Calif., March 31, 2010 — GlaxoSmithKline (NYSE: GSK) and Isis Pharmaceuticals Inc. (Nasdaq: ISIS) announced today a new strategic alliance that will apply the Isis antisense drug discovery platform to seek out and develop new therapeutics against targets for rare and serious disease, including infectious diseases and some conditions causing blindness.

Under the terms of the agreement, which covers up to six programs, Isis will receive an upfront $35 million payment from GSK and is eligible to receive on average up to $20 million in milestones per program up to Phase 2 proof of concept (PoC). GSK will have the option to license compounds at PoC, and will be responsible for all further development and commercialization. Isis will be eligible to receive license fees and milestone payments, totaling nearly $1.5 billion, in the event all six programs are successfully developed for one or more indications and commercialized through to pre-agreed sales targets. In addition Isis will receive up to double-digit royalties on sales, from any product that is successfully commercialized.

“As a platform, the Isis antisense approach offers us an exciting opportunity to target certain severe diseases in a way that has not previously been possible,” said Dr. Patrick Vallance, Senior Vice-President and Head of Drug Discovery at GSK. “Isis Pharmaceuticals is a leader in antisense technology, and this new alliance will enhance our discovery platform in this promising research area.”

Antisense therapies target the proteins involved in disease processes through the RNA that is involved in building these proteins. The Isis discovery platform develops specific therapies that bind to messenger RNA (mRNA) and inhibit the production of disease-causing proteins. Isis recently announced data from a Phase 3 trial in heterozygous familial hypercholesterolemia patients that demonstrated the therapeutic effect of this approach.

This alliance provides GSK with access to Isis’ expertise in drug discovery and development of RNA-targeted therapeutics, with Isis retaining responsibility for the discovery and development of compounds to the alliance targets from inception to POC.

“We are excited to be working with GSK to apply antisense technology to these new therapeutic areas. We are particularly excited to work on the novel targets GSK brought to the alliance,” said Dr. Stanley T. Crooke, Chairman and Chief Executive Officer for Isis Pharmaceuticals. “This alliance is exactly the type of deal we want to do. We retain control of the discovery and early development of our drugs while working together with a very high-quality partner to maximize the value of the drugs in late-stage development and commercialization.”

Isis will hold an investor conference call and live audio webcast today, March 31, 2010 at 8:30 a.m. ET to provide detailed information on its new strategic alliance with GSK.

About RNA-targeted therapeutics

RNA-targeted therapeutics, or antisense therapies such as oligonucleotides, represents an opportunity for a new drug class. Where most other medicines are small molecules or biologics that target a specific protein in a diseases process, antisense therapies prevent protein synthesis by eliminating the mRNA - the template or pattern that guides the production of the protein.

About Isis Pharmaceuticals

Isis is exploiting its expertise in RNA to discover and develop novel drugs for its product pipeline and for its partners. The Company has successfully commercialized the world’s first antisense drug and has 22 drugs in development. Isis’ drug development programs are focused on treating cardiovascular, metabolic, and severe neurodegenerative diseases and cancer. Isis’ partners are developing antisense drugs invented by Isis to treat a wide variety of diseases. Isis and Alnylam Pharmaceuticals are joint owners of Regulus Therapeutics Inc., a company focused on the discovery, development and commercialization of microRNA therapeutics. Isis also has made significant innovations beyond human therapeutics resulting in products that other companies, including Abbott, are commercializing. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of over 1,600 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

About GlaxoSmithKline

GlaxoSmithKline — one of the world’s leading research-based pharmaceutical and healthcare companies — is committed to improving the quality of human life by enabling people to do more, feel better and live longer.

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GSK Cautionary statement regarding forward-looking statements

Under the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995, GSK cautions investors that any forward-looking statements or projections made by GSK, including those made in this announcement, are subject to risks and uncertainties that may cause actual results to differ materially from those projected. Factors that may affect GSK’ s operations are described under ‘Risk Factors’ in the ‘Business Review’ in the company’ s Annual Report on Form 20-F for 2008.

Isis Safe Harbor Statement

This press release includes forward-looking statements regarding Isis’ strategic alliance with GSK, and Isis’ research and development opportunities in disease areas including rare and infectious diseases. Any statement describing Isis’ goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such products. Isis’ forward-looking statements also involve assumptions that, if they never materialize or prove correct, could

cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Isis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' programs are described in additional detail in Isis' annual report on Form 10-K for the year ended December 31, 2009, which is on file with the SEC. Copies of this and other documents are available from the Company.

SCHEDULE 12.4.1

Applicable Option Exercise Payments in Change of Control

[***]

EXHIBIT 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Isis Pharmaceuticals, Inc.;

2. Based on my knowledge, this quarterly report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this quarterly report;

3. Based on my knowledge, the condensed consolidated financial statements, and other financial information included in this quarterly report, fairly present in all material respects the financial condition, condensed consolidated results of operations and condensed consolidated cash flows of the registrant as of, and for, the periods presented in this quarterly report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: May 6, 2010

/s/ Stanley T. Crooke

Stanley T. Crooke, M.D., Ph.D.
Chief Executive Officer

EXHIBIT 31.2

CERTIFICATION

I, B. Lynne Parshall, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Isis Pharmaceuticals, Inc.;

2. Based on my knowledge, this quarterly report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this quarterly report;

3. Based on my knowledge, the condensed consolidated financial statements, and other financial information included in this quarterly report, fairly present in all material respects the financial condition, condensed consolidated results of operations and condensed consolidated cash flows of the registrant as of, and for, the periods presented in this quarterly report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: May 6, 2010

/s/ B. Lynne Parshall

B. Lynne Parshall, J.D.
Chief Financial Officer

Exhibit 32.1

CERTIFICATION

Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, Stanley T. Crooke, the Chief Executive Officer of Isis Pharmaceuticals, Inc., (the "Company"), and B. Lynne Parshall, the Chief Financial Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

1. The Company's Quarterly Report on Form 10-Q for the period ended March 31, 2010, to which this Certification is attached as Exhibit 32.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

2. The information contained in the Periodic Report fairly presents, in all material respects, the financial condition of the Company at the end of the period covered by the Periodic Report and the results of operations of the Company for the period covered by the Periodic Report.

Dated: May 6, 2010

/s/ Stanley T. Crooke	/s/ B. Lynne Parshall
Stanley T. Crooke, M.D., Ph.D.	B. Lynne Parshall, J.D.
Chief Executive Officer	Chief Financial Officer

A signed original of this written statement required by Section 906 has been provided to Isis Pharmaceuticals, Inc. and will be retained by Isis Pharmaceuticals, Inc. and furnished to the Securities and Exchange Commission or its staff upon request.