Table of Contents

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 June 30, 2008

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 is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See definitions 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 August 4, 2008 was 95,645,014.

Table of Contents

ISIS PHARMACEUTICALS, INC.
FORM 10-Q

INDEX

TRADEMARKS

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

Table of Contents

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

	June 30, 2008 (Unaudited)	December 31, 2007
ASSETS		
Current assets:		
Cash and cash equivalents	$ 445,720	$ 138,614
Short-term investments	91,249	55,105
Contracts receivable	6,399	6,177
Inventories	4,699	2,817
Other current assets	7,113	4,604
Total current assets	555,180	207,317
Property, plant and equipment, net	10,494	7,131
Licenses, net	17,958	19,100
Patents, net	18,538	17,759
Deposits and other assets	7,229	7,551
Total assets	$ 609,399	$ 258,858

LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 5,716	$ 4,507
Accrued compensation	3,631	10,461
Accrued liabilities	7,441	6,794
Derivative instrument related to Abbott's call option	5,147	—
Current portion of long-term obligations	3,669	7,238
Current portion of deferred contract revenue	101,507	33,205
Total current liabilities	127,111	62,205
2 5/8% convertible subordinated notes	162,500	162,500
Long-term obligations, less current portion	5,415	362
Long-term deferred contract revenue	214,202	23,548
Total liabilities	509,228	248,615
Noncontrolling interest in Regulus Therapeutics LLC	7,523	9,371
Noncontrolling interest in Ibis Biosciences, Inc.	33,625	—
Stockholders' equity:		
Common stock, $0.001 par value; 200,000,000 shares authorized, 95,445,661 and 87,239,423 shares issued and outstanding at June 30, 2008 and December 31, 2007, respectively	95	87
Additional paid-in capital	890,435	827,992
Accumulated other comprehensive income	2,730	538
Accumulated deficit	(834,237)	(827,745)
Total stockholders' equity	59,023	872
Total liabilities, noncontrolling interest and stockholders' equity	$ 609,399	$ 258,858

See accompanying notes

Table of Contents

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2008	2007	2008	2007
Revenue:				
Research and development revenue under collaborative agreements	$ 26,814	$ 3,482	$ 47,499	$ 5,484
Licensing and royalty revenue	6,147	331	6,815	779
Total revenue	32,961	3,813	54,314	6,263
Expenses:				
Research and development	31,195	20,384	57,642	40,333
Selling, general and administrative	4,899	3,089	8,635	6,491
Total operating expenses	36,094	23,473	66,277	46,824
Loss from operations	(3,133)	(19,660)	(11,963)	(40,561)
Other income (expense):				
Investment income	560	3,053	5,515	6,454
Interest expense	(1,391)	(2,016)	(2,788)	(4,644)
Gain on investments	—	1,989	—	3,510
Loss on early retirement of debt	—	(1,993)	—	(3,212)
Loss attributed to noncontrolling interest in Symphony GenIsis, Inc.	—	7,603	—	14,409
Loss attributed to noncontrolling interest in Regulus Therapeutics LLC	965	—	1,848	—
Loss attributed to noncontrolling interest in Ibis Biosciences, Inc.	791	—	896	—
Net loss applicable to common stock	$ (2,208)	$ (11,024)	$ (6,492)	$ (24,044)
Basic and diluted net loss per share	$ (0.02)	$ (0.13)	$ (0.07)	$ (0.29)
Shares used in computing basic and diluted net loss per share	94,675	82,548	92,737	82,502

See accompanying notes.

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

	Six Months Ended June 30,	
	2008	2007
Net cash provided by (used in) operating activities	$ 252,756	$ (22,166)
Investing activities:		
Purchases of short-term investments	(129,033)	(59,578)
Proceeds from the sale of short-term investments	92,728	69,098
Purchases of property, plant and equipment	(4,209)	(967)
Acquisition of licenses and other assets	(1,253)	(1,216)
Proceeds from the sale of strategic investments	—	5,181
Net cash provided by (used in) investing activities	(41,767)	12,518
Financing activities:		
Net proceeds from issuance of equity	4,724	1,872
Proceeds from issuance of convertible promissory note to GSK	5,000	—
Proceeds from issuance of 2 5/8% convertible subordinated notes, net of issuance costs	—	157,056
Principal and redemption premium payment on prepayment of the 5 1/2% convertible subordinated notes	—	(127,021)
Principal payments on debt and capital lease obligations	(3,569)	(3,809)
Proceeds from stock purchase by Genzyme Corporation, net of fees	49,962	—
Proceeds from capital contributions to Ibis Biosciences, Inc.	40,000	—
Net cash provided by financing activities	96,117	28,098
Net increase in cash and cash equivalents	307,106	18,450
Cash and cash equivalents at beginning of period	138,614	114,514
Cash and cash equivalents at end of period	$ 445,720	$ 132,964
Supplemental disclosures of cash flow information:		
Interest paid	$ 2,308	$ 3,381
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 1,467	$ 544

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
June 30, 2008
(Unaudited)

1. Basis of Presentation

The unaudited interim condensed consolidated financial statements for the three and six month periods ended June 30, 2008 and 2007 have been prepared on the same basis as the audited financial statements for the year ended December 31, 2007. 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, 2007 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"), our wholly owned subsidiaries, Isis Pharmaceuticals Singapore Pte Ltd., Isis USA Ltd. and Symphony GenIsis, Inc. In addition to our wholly owned subsidiaries, our condensed consolidated financial statements include two variable interest entities, Ibis Biosciences, Inc. and Regulus Therapeutics LLC, for which we are the primary beneficiary as defined by Financial Accounting Standards Board Interpretation ("FIN") 46R (revised 2003), *Consolidation of Variable Interest Entities, an Interpretation of ARB 51*. All significant intercompany balances and transactions have been eliminated.

2. Significant Accounting Policies

Revenue recognition

We follow the provisions as set forth by Staff Accounting Bulletin ("SAB") 101, *Revenue Recognition in Financial Statements*, SAB 104, *Revenue Recognition*, and Financial Accounting Standards Board Emerging Issues Task Force ("EITF") 00-21, *Accounting for Revenue Arrangements with Multiple Deliverables*.

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, the amounts are included in deferred revenue on the consolidated balance sheet.

Research and development revenue under collaborative agreements

We often enter into collaborations where 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. Should different estimates prevail, revenue recognized could be materially different. To date our estimates have not required material adjustments. 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 activities to be performed 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 date 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, as defined by 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 and we are not obligated for future performance related to the achievement of the milestone.

Table of Contents

We generally recognize revenue related to the sale of our drug inventory as we ship or deliver drugs to our partners. In several instances, we completed the manufacturing of drugs, but our partners asked us to deliver the drug on a later date. Under these circumstances, we ensured that the provisions in SAB 104 were met before we recognized the related revenue.

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.

In the fourth quarter of 2006, we started to sell the Ibis T5000 Biosensor System commercially. The sale of each Ibis T5000 Biosensor System contains multiple elements. Since we had no previous experience commercially selling the Ibis T5000 Biosensor System, we had no basis to determine the fair values of the various elements included in each system; therefore, we account for the entire system as one deliverable and recognize revenue over the period of performance. The assay kits, which are sold separately from the instrument, are considered part of the system from an accounting perspective because the assay kits and the instrument are dependent on each other. For a one-year period following the sale, we have ongoing support obligations for the Ibis T5000 Biosensor System; therefore, we are amortizing the revenue for the entire system, including related assay kits, over a one-year period. Once we obtain a sufficient number of sales to enable us to identify each element's fair value, we will be able to recognize revenue separately for each element.

As part of our Genzyme strategic alliance, in February 2008 Genzyme Corporation made a $150 million equity investment in us by purchasing 5 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 represents 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 ratably into revenue until June 2012, which represents the end of our performance obligation based on the research and development plan included in the agreement. See further discussion about our collaboration with Genzyme in *Note 5*, *Collaborative Arrangements and Licensing Agreements*.

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 future significant performance obligations and are reasonably assured of collecting the resulting receivable.

Short-term investments

We have equity investments in privately- and publicly-held biotechnology companies. We hold ownership interests of less than 20% in each of the respective entities. 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 issuer, near term prospects of the issuer and our current need for cash. Unrealized gains and losses related to temporary declines are recorded as a separate component of stockholders' equity. When we determine that a decline in value is other-than-temporary, we recognize an impairment loss in the period in which the other-than-temporary decline occurs. We determined that there were no other-than-temporary declines in value of our investments in the first half of 2008 and 2007. During the first half of 2007, we sold the remainder of our equity securities of Alnylam Pharmaceuticals, Inc. that we owned resulting in a realized gain of $3.5 million.

Inventory valuation

In accordance with Statement of Financial Accounting Standards ("SFAS") 2, *Accounting for Research and Development Costs*, 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 and related manufacturing 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. Each of our raw materials can be used in multiple products and, as a result, has future economic value independent of the development status of any single drug. For example, if one of our drugs failed, the raw materials allocated for that drug could be used 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. Also included in inventory are material costs, labor costs and manufacturing overhead costs associated with the Ibis T5000 Biosensor System and related assay kits. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out

Table of Contents

method. We review inventory periodically and reduce the carrying value of items considered to be slow moving or obsolete to their estimated net realizable value. We consider several factors in 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 half of 2008 and 2007.

Total inventory includes the following as of June 30, 2008 and December 31, 2007 (in thousands):

	June 30, 2008	December 31, 2007
Raw materials	$ 4,411	$ 2,679
Work-in-process	288	138
	$ 4,699	$ 2,817

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 determine 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, if appropriate. We amortize patent costs over their estimated useful lives of ten years, beginning with the date the patents are issued. For the first half of 2008 and 2007, we recorded a non-cash charge of $679,000 and $337,000, respectively, which was included in research and development expenses and was related to the assignment of patents to certain of our partners and the write-down of our patent costs to their estimated net realizable values.

Long-lived assets

We assess the value of our long-lived assets, which include property, plant and equipment, patent costs, and licenses acquired from third parties, under the provisions set forth by SFAS 144, *Accounting for the Impairment or Disposal of Long-Lived Assets*, and we evaluate our long-lived assets for impairment on at least a quarterly basis.

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.

Consolidation of variable interest entities

We have implemented the provisions of FIN 46R, which addresses consolidation by business enterprises of 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 June 30, 2008, we had collaborative arrangements with nine entities that we consider to be variable interest entities under FIN 46R. For the first half of 2008, our condensed consolidated financial statements include two variable interest entities, Ibis and Regulus, for which we are the primary beneficiary. For the first half of 2007, our condensed consolidated financial statements include two variable interest entities, Ibis and Symphony GenIsis, for which we were the primary beneficiary. Until our acquisition of Symphony GenIsis in September 2007, we identified Symphony GenIsis as a variable interest entity that we consolidated.

Table of Contents

Comprehensive loss

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2008	2007	2008	2007
Comprehensive loss:				
Unrealized holding gains (losses)	$ 607	$ 67	$ 2,192	$ (713)
Reclassification adjustment for realized gains included in net income	—	(1,730)	—	(3,147)
Net loss applicable to common stock	(2,208)	(11,024)	(6,492)	(24,044)
Comprehensive loss	$ (1,601)	$ (12,687)	$ (4,300)	$ (27,904)

Stock-based compensation expense

We account for our stock-based compensation expense related to employee stock options and employee stock purchases under SFAS 123R, *Share-Based Payment*. We estimate the fair value of each stock option granted to employees 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. For the stock options granted subsequent to January 1, 2008, we estimated the expected term of options granted based on historical exercise patterns. For the stock options granted prior to January 1, 2008, the estimated expected term is a derived output of the simplified method, as allowed under SAB 107.

For the six months ended June 30, 2008 and 2007, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Six Months Ended June 30,	
	2008	2007
Risk-free interest rate	3.1%	4.7%
Dividend yield	0.0%	0.0%
Volatility	55.0%	63.7%
Expected Life	4.6 years	4.6 years

ESPP:

	Six Months Ended June 30,	
	2008	2007
Risk-free interest rate	3.3%	5.1%
Dividend yield	0.0%	0.0%
Volatility	56.7%	56.1%
Expected Life	6 months	6 months

We record stock options granted to non-employees, which consist primarily of options granted to Regulus' Scientific Advisory Board, at their fair value in accordance with the requirements of SFAS 123R, then periodically remeasure them in accordance with EITF 96-18, *Accounting for Equity Instruments that are Issued to Other Than Employees for Acquiring, or in Conjunction with Selling, Goods or Services*, and recognize the expense over the service period.

Stock-based compensation expense for the three and six months ended June 30, 2008 and 2007 (in thousands, except per share data) was allocated as follows:

	Three Months Ended June 30,		Six Months Ended June 30,	
	2008	2007	2008	2007
Research and development	$ 3,191	$ 1,952	$ 6,267	$ 3,878
Selling, general and administrative	815	437	1,498	875
Non-cash compensation expense related to stock options included in operating expenses	$ 4,006	$ 2,389	$ 7,765	$ 4,753
Stock-based compensation expense, per share:				
Basic and diluted	$ (0.04)	$ (0.03)	$ (0.08)	$ (0.06)

Table of Contents

As part of the Regulus joint venture, both we and Alnylam issued our own company's stock options to members of Regulus' Board of Directors and Scientific Advisory Board. The expenses associated with these options are recorded on Regulus' books. Since we are consolidating the financial results of Regulus, $681,000 and $1.1 million of non-cash stock based compensation expense associated with these options for the three and six months ended June 30, 2008 was included in our consolidated expenses.

As of June 30, 2008, total unrecognized compensation cost related to non-vested stock-based compensation plans was $18.6 million. Total unrecognized compensation cost will be adjusted 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 December 2007, the Financial Accounting Standards Board ("FASB") issued SFAS 160, *Noncontrolling Interests in Consolidated Financial Statements, an amendment to ARB No. 51*. This statement states that accounting and reporting for minority interests will be recharacterized as noncontrolling interests and classified as a component of equity. SFAS 160 applies to all entities that prepare consolidated financial statements, but will affect only those entities that have an outstanding noncontrolling interest in one or more subsidiaries or that deconsolidate a subsidiary. This statement is effective for fiscal years beginning after December 15, 2008, which will be effective for our fiscal year 2009. We do not expect the adoption of SFAS 160 to have a material impact on our results of operations and financial position but the retrospective presentation requirements of SFAS 160 will impact how noncontrolling interests are presented in our consolidated financial statements.

In May 2008, FASB issued Staff Position No. APB 14-1, *Accounting for Convertible Debt Instruments That May be Settled in Cash upon Conversion (Including Partial Cash Settlement)*, ("FSP No. APB 14-1"). This statement states that convertible debt instruments that may be settled in cash upon conversion (including partial cash settlement) should separate the liability and equity components of the instruments in a manner that will reflect the entity's nonconvertible debt borrowing rate when interest cost is recognized in subsequent periods. FSP No. APB 14-1 will require that the value assigned to the debt component be equal to the estimated fair value of a similar debt instrument without the conversion feature, which results in the debt being recorded at a discount. The resulting debt discount will be amortized over the period during which the debt is expected to be outstanding as additional non-cash interest expense. This opinion is effective for fiscal years beginning on or after December 15, 2008, which will be effective for our fiscal year 2009, and must be

applied retrospectively to all periods presented. We are currently evaluating what the impact of adopting FSP No. APB 14-1 will have on our consolidated financial statements.

In June 2008, the EITF issued EITF 07-05, *Determining Whether an Instrument (or Embedded Feature) Is Indexed to an Entity's Own Stock*. EITF 07-05 clarifies the determination of whether an instrument (or an embedded feature) is indexed to an entity's own stock, which would qualify as a scope exception under SFAS 133, *Accounting for Derivative Instruments and Hedging Activities*. EITF 07-05 is effective for financial statements issued for fiscal years beginning after December 15, 2008, which will be effective for our fiscal year 2009. Early adoption for an existing instrument is not permitted. We are currently evaluating what the impact of adopting EITF 07-05 will have on our consolidated financial statements.

3. Fair Value Measurements

In September 2006, the FASB issued SFAS 157, *Fair Value Measurements*. SFAS 157 defines fair value, establishes a framework for measuring fair value in accordance with accounting principles generally accepted in the United States, and expands disclosures about fair value measurements. We have adopted the provisions of SFAS 157 as of January 1, 2008. Although the adoption of SFAS 157 did not impact our financial condition, results of operations, or cash flow, we are now required to provide additional disclosures as part of our financial statements.

SFAS 157 establishes a three-tier fair value hierarchy, which prioritizes the inputs used in measuring fair value. These tiers include: Level 1, defined as observable inputs such as quoted prices in active markets, which includes our 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 auction rate security 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, which includes the derivative instruments related to the subscription right and call option granted to Abbott Molecular Inc.

The fair value of the assets and liabilities required to be measured at fair value on a recurring basis was determined using the following inputs in accordance with SFAS 157 at June 30, 2008 (in thousands):

	Total	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Available-for-sale securities (1)	$ 505,959	$ 503,686	$ 2,273	$ —
Derivative instrument (2)	5,147	—	—	5,147(4)
Equity securities (3)	3,841	3,841	—	—
Total	$ 514,947	$ 507,527	$ 2,273	$ 5,147

Table of Contents

(1) Included in cash and cash equivalents and short term investments on our Condensed Consolidated Balance Sheet.

(2) Included in current liabilities on our Condensed Consolidated Balance Sheet.

(3) Included in other current assets and deposits and other assets on our Condensed Consolidated Balance Sheets.

(4) Represents the derivative instrument related to the call option granted to Abbott. As of June 30, 2008, the derivative instrument line item did not include the subscription right as it was exercised on June 27, 2008 (see additional discussion in Note 5).

The following table presents a reconciliation of the assets and liabilities measured at fair value on a recurring basis using significant unobservable inputs (Level 3) from December 31, 2007 to June 30, 2008 (in thousands):

	Derivative Instruments
Balance at December 31, 2007	$ —
Issuance of derivative instruments	5,376(1)
Adjustment to fair value included in earnings	(179)(2)
Exercise of derivative instrument	(50)(3)
Balance at June 30, 2008	$ 5,147

1) Represents the derivative instruments related to the subscription right and call option granted to Abbott (see additional discussion in Note 5).

2) The subscription right and call option granted to Abbott are revalued at the end of each reporting period until they expire or are exercised. The resulting difference in fair value is included in our results of operations. For the first half of 2008, the adjustment to fair value resulted in a gain and was included in investment income.

3) The subscription right was exercised by Abbott on June 27, 2008 (see additional discussion in Note 5).

Additionally, in February 2007, the FASB issued SFAS 159, *The Fair Value Option for Financial Assets and Financial Liabilities*. This statement allows entities to account for most financial instruments at fair value rather than under other applicable GAAP, such as historical cost. Under SFAS 159, an asset or liability is required to be marked to fair value every reporting period with the gain or loss from a change in fair value recorded in the statement of operations. We adopted the provisions of SFAS 159 in the first quarter of 2008. SFAS 159 permits companies to make an election to carry certain eligible financial assets and liabilities at fair value. We have made the election not to measure any additional assets and liabilities at fair value other than our available-for-sale and equity securities that are currently required by SFAS 115, *Accounting for Certain Investments in Debt and Equity Securities* and our

derivative instrument that is currently required under SFAS 133, *Accounting for Derivative Instruments and Hedging Activities*, to be revalued at fair value each reporting period. Therefore, the adoption of SFAS 159 did not impact our results of operations, financial position or cash flows.

4. Long-Term 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 $2^5/_8$%, which is payable semi-annually. The $2^5/_8$% 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 the $2^5/_8$% notes at a redemption price equal to 100.75% of the principal amount between February 15, 2012 and February 14,

Table of Contents

2013; 100.375% of the principal amount between February 15, 2013 and February 14, 2014; and 100% of the principal amount thereafter. Holders of the $2^5/_8$% notes also are able to require us to repurchase these notes on February 15, 2014, February 15, 2017 and February 15, 2022, and upon the occurrence of certain defined conditions, at 100% of the principal amount of the $2^5/_8$% notes being repurchased plus accrued interest and unpaid interest.

We used the net proceeds from the issuance of the $2^5/_8$% notes to repurchase our $5^1/_2$% convertible subordinated notes due in 2009. In January 2007, we repurchased approximately $44.2 million aggregate principal amount of our $5^1/_2$% notes at a redemption price of $44.9 million plus accrued but unpaid interest. In May 2007, we redeemed the remaining $80.8 million principal balance at a redemption price of $82.1 million plus accrued but unpaid interest. As a result of the repayment of these notes, we recognized a $3.2 million loss on the early extinguishment of debt in the first half of 2007, which included a $1.2 million non-cash write-off of unamortized debt issuance costs.

5. Collaborative Arrangements and Licensing Agreements

The information discussed below represents partnerships we entered into during 2008. There have been no material changes to the partnerships entered into prior to 2008 from the information provided in Note 6—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, 2007.

Pharmaceutical Alliances and Licensing

Genzyme Corporation

In January 2008, we entered into a strategic alliance with Genzyme focused on the licensing of mipomersen and a research relationship. The transaction included a $175 million licensing fee, a $150 million equity investment in us (5 million shares of our common stock at $30 per share), over $1.5 billion in milestone payments and a share of profits on mipomersen and follow-on drug(s) ranging from 30 to 50 percent of all commercial sales. Under this alliance, we will over time transition the development responsibility to Genzyme and Genzyme will be responsible for the commercialization of mipomersen. We will contribute 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.

Genzyme has agreed that it will not sell its equity investment in Isis stock purchased in February 2008 until the earlier of four years from the date of our mipomersen license agreement, the first commercial sale of mipomersen and the termination of our mipomersen license agreement. Thereafter, Genzyme will be subject to monthly limits on the number of shares it can sell. In addition, Genzyme has agreed that until the earlier of the 10 year anniversary of the mipomersen license agreement and the date Genzyme holds less than 2% of our issued and outstanding common stock, Genzyme will not acquire any additional shares of our common stock without our consent.

The price Genzyme paid for our common stock represented a significant premium over the fair value of our common stock. Using a Black-Scholes option valuation model, we determined that the value of the premium was $100 million, which represents value Genzyme gave to us to help fund the companies' research collaboration that began in January 2008. We are amortizing this premium along with the $175 million licensing fee that we received in the second quarter of 2008 ratably into revenue until June 2012, which represents the end of our performance obligation based on the research and development plan included in the agreement. For the three and six months ended June 30, 2008, we recognized revenue of $8.7 million and $15.0 million, respectively, related to the $100 million premium and the $175 million licensing fee, which represented 28% of our total revenue for the first half of 2008. Our Condensed Consolidated Balance Sheet at June 30, 2008 includes deferred revenue of $260.0 million, which represents the remaining premium and licensing fee.

Drug Discovery and Development Satellite Company Collaborations

Antisense Therapeutics Limited

In December 2001, we licensed ATL/TV1102 to ATL, an Australian company publicly traded on the Australian Stock Exchange and in February 2008, ATL licensed ATL/TV1102 to Teva Pharmaceutical Ltd. As part of our licensing agreement with ATL, we will receive one third of sublicense fees and milestone payments ATL receives from Teva as well as a percentage of any royalties. As a result of the encouraging data that ATL and Teva reported from a Phase 2a study on ATL/TV1102 in patients with relapsing and remitting multiple sclerosis, we earned $1.4 million as our portion of ATL's licensing fee and milestone payment from Teva which we included in revenue in the second quarter of 2008.

Table of Contents

In addition to ATL/TV1102, ATL is currently developing ATL1103 for growth and sight disorders. ATL1103 is a product of our joint antisense drug discovery and development collaboration, which we extended for an additional two years in January 2007. ATL pays us for access to our antisense expertise

and for research and manufacturing services we may provide to ATL during the collaboration. Additionally, ATL will pay royalties to us on any antisense drugs discovered and developed within the partnership.

In connection with this collaboration, we received 30.0 million shares of ATL common stock upon completion of ATL's initial public offering, representing an initial ownership percentage of approximately 14%. The initial ATL common stock we received had a value of $2.8 million, and we recognized this amount into revenue ratably over the five-year period of performance under the collaboration, which ended in November 2006. There were no changes in our period of performance. Our Condensed Consolidated Balance Sheets at June 30, 2008 and December 31, 2007 include deferred revenue of $432,000 and $250,000, respectively. For the three and six months ended June 30, 2008, we recorded revenue of $1.4 million related to this collaboration compared to $44,000 and $55,000 for the same periods in 2007. As of June 30, 2008 and December 31, 2007, our ownership percentage in ATL, including 10.3 million shares we purchased subsequent to shares we acquired in ATL's initial public offering, was less than 10% of ATL's equity. Our balance sheets at June 30, 2008 and December 31, 2007 included a short-term investment at fair market value of $2.7 million and $1.4 million, respectively, related to this equity investment.

Ibis Collaborations

Abbott Molecular Inc.

In January 2008, we, Ibis and Abbott entered into a strategic alliance master agreement pursuant to which:

- Abbott purchased Ibis common stock representing approximately 10.25% of the issued and outstanding common stock of Ibis for a total purchase price of $20 million;
- Ibis granted Abbott a subscription right to purchase an additional $20 million of Ibis common stock before July 31, 2008, which when combined with Abbott's initial investment would represent approximately 18.6% of the issued and outstanding common stock of Ibis. On June 27, 2008, Abbott exercised this subscription right by purchasing an additional $20 million of Ibis common stock;
- We granted Abbott a call option to acquire from us all remaining Ibis capital stock for a purchase price of $175 million, which, subject to Ibis satisfying a defined set of objectives, may be increased to as much as $190 million;
- If Abbott ultimately acquires Ibis under the call option agreement, Abbott will make the earn out payments described below, which will enable our shareholders to continue to benefit from Ibis' success.

The investment by Abbott provides Ibis the funding to take the key next steps in enhancing its value, while allowing it to remain independent and focused during the option period so as to best enable this progress. This alliance with Abbott also provides Ibis the benefit of an experienced partner in molecular diagnostics and will focus Ibis on commercial success.

If Abbott acquires from us all of the remaining Ibis capital stock under the call option, Abbott will pay us earn out payments equal to a percentage of Ibis' revenue related to sales of Ibis T5000 Biosensor Systems, including instruments, assay kits and successor products from the date of the final acquisition through December 31, 2025. These earn out payments will equal 5% of Ibis' cumulative net sales over $150 million and up to $2.1 billion, and 3% of Ibis' cumulative net sales over $2.1 billion. The earn out payments may be reduced from 5% to as low as 2.5% and from 3% to as low as 1.5%, respectively, upon the occurrence of certain events. In addition, as part of the final acquisition, Ibis will distribute to us, immediately prior to the closing, all of Ibis' cash on hand and any receivables or other payments due to Ibis under government contracts and grants held by Ibis as of the closing.

The call option initially expires on December 31, 2008, provided that, subject to certain conditions, Abbott may extend the term of the call option through June 30, 2009.

Table of Contents

Until the expiration of the call option, we and Ibis must obtain Abbott's consent before we or Ibis can take specified actions, such as amending Ibis' certificate of incorporation, redeeming, repurchasing or paying dividends on Ibis' capital stock, issuing any Ibis capital stock, entering into a transaction for the merger, consolidation or sale of Ibis, creating any Ibis indebtedness, or entering into any Ibis strategic alliance, joint venture or joint marketing agreement. In addition, the strategic alliance contains a make whole provision such that in the event of a liquidation or change of control of Ibis, Abbott will receive a payment equal to the price paid per share of the capital stock of Ibis acquired by Abbott in the initial investment and under the subscription right, plus a yield of 3% annually from the date Abbott purchased the Ibis common stock, prior to the distribution of any proceeds to any other holders of Ibis capital stock.

We valued each element of the initial transaction and as a result allocated $14.6 million to the initial stock purchase with the remaining $5.4 million allocated to the call option and the subscription right (the "Derivative Instruments"). On June 27, 2008, Abbott exercised its subscription right and purchased an additional $20 million of Ibis' common stock. As a result of Abbott's investments in Ibis, Abbott is a minority owner of Ibis. Therefore, the cumulative value attributed to the initial and subsequent stock purchase of $34.6 million was recorded as a "Noncontrolling Interest in Ibis Biosciences, Inc." on our Condensed Consolidated Balance Sheet. As the strategic alliance progresses, this line item will be reduced by Abbott's share of Ibis' net losses, which were $896,000 in the first half of 2008, until the balance becomes zero. The reductions to the Noncontrolling Interest in Ibis will be reflected in our Condensed Consolidated Statement of Operations using a similar caption and will improve our reported net loss. At the close of the initial transaction, $5.4 million of combined value attributed to the derivative instruments was included in the current liabilities section of our Condensed Consolidated Balance Sheet. As required by current accounting rules, we revalue the derivative instruments at the end of each quarter until they expire or are exercised. Since Abbott exercised the subscription right on June 27, 2008, the remaining liability of $5.1 million represents the fair value of only the call option at June 30, 2008.

In addition to the previously mentioned items, Ibis and Abbott have entered into two other important transactions, which enhance the two companies' strategic alliance. In the second quarter of 2008, Abbott entered into a distribution agreement with Ibis by paying Ibis $480,000 in the form of an up-front payment for the right to be an non-exclusive distributor for the marketing, promotion, solicitation, sales and distribution of Ibis assay kits and Ibis T5000 Biosensor Systems to customers worldwide. Most recently in the third quarter of 2008, Ibis entered into a consulting agreement with Abbott primarily focused on advancing the regulatory work and implementing the quality systems necessary for Ibis to enter into the clinical diagnostics market.

Regulus Collaborations

In April 2008, Regulus entered into a strategic alliance with GlaxoSmithKline to discover, develop and market 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 developed under each program by Regulus 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.

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 common 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 is not repaid in cash after three years, we, Alnylam and Regulus may elect to repay the note plus interest with shares of each company's common stock. Regulus could also be eligible to receive 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 addition to the potential of up to nearly $600 million Regulus could receive in option, license and milestone payments, Regulus would also receive tiered royalties up to double digits on worldwide sales of drugs resulting from the alliance.

The $15 million option fee is being amortized into revenue over Regulus' six year period of performance. The $5 million note is shown as a liability on our Condensed Consolidated Balance Sheet. For the three and six months ended June 30, 2008, we recognized revenue of $625,000 related to the $15 million option fee, which represented 1% of our total revenue for the first half of 2008. Our Condensed Consolidated Balance Sheet at June 30, 2008 includes deferred revenue of $14.4 million, which represents the remaining option fee.

Table of Contents

6. Segment Information and Concentration of Business Risk

Segment information

We report our financial results in three reportable segments, Drug Discovery and Development, Ibis and Regulus. Segment loss from operations includes revenue offset by research and development expenses, cost of commercial revenue for our Ibis subsidiary, selling, general and administrative expenses, and other charges 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 Ibis subsidiary generates revenue from grants and contracts from United States government agencies, from sales of its Ibis T5000 Biosensor System and related assay kits and the analysis of samples within its assay services laboratory.

Our Regulus joint venture generates revenue from research grants and collaborations with corporate partners such as the recently announced strategic alliance with GSK in April 2008.

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

	Drug Discovery and Development	Ibis	Regulus	Total
Three Months Ended June 30, 2008				
Revenue:				
Research and development	$ 22,900	$ 2,160	$ 656	$ 25,716
Commercial revenue (1)	—	1,098	—	1,098
Licensing and royalty	6,147	—	—	6,147
Total segment revenue	$ 29,047	$ 3,258	$ 656	$ 32,961
Income (loss) from operations	$ 4,150	$ (5,416)	$ (1,867)	$ (3,133)
Three Months Ended June 30, 2007				
Revenue:				
Research and development	$ 1,591	$ 1,081	$ —	$ 2,672
Commercial revenue (1)	—	810	—	810
Licensing and royalty	331	—	—	331
Total segment revenue	$ 1,922	$ 1,891	$ —	$ 3,813
Loss from operations	$ (16,790)	$ (2,870)	$ —	$ (19,660)
Six Months Ended June 30, 2008				
Revenue:				
Research and development	$ 40,514	$ 3,944	$ 748	$ 45,206
Commercial revenue (1)	—	2,293	—	2,293
Licensing and royalty	6,815	—	—	6,815
Total segment revenue	$ 47,329	$ 6,237	$ 748	$ 54,314
Income (loss) from operations		)	)	)

	$ 652	$ (9,313	$ (3,302	$ (11,963
Total assets as of June 30, 2008	$ 538,055	$ 43,670	$ 27,674	$ 609,399
Six Months Ended June 30, 2007				
Revenue:				
Research and development	$ 2,017	$ 2,026	$ —	$ 4,043
Commercial revenue (1)	—	1,441	—	1,441
Licensing and royalty	779	—	—	779
Total segment revenue	$ 2,796	$ 3,467	$ —	$ 6,263
Loss from operations	$ (34,557)	$ (6,004)	$ —	$ (40,561)
Total assets as of December 31, 2007	$ 239,099	$ 9,313	$ 10,446	$ 258,858

(1) Ibis' commercial revenue has been classified as research and development revenue under collaborative agreements on our Condensed Consolidated Statements of Operations.

Table of Contents

Concentrations of business risk

We have historically funded our operations in part from collaborations with corporate partners and as it relates to Ibis, from collaborations with various government agencies. Additionally, beginning in the second half of 2006, Ibis began selling commercial products and services. A relatively small number of partners historically 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 June 30,		Six Months Ended June 30,	
	2008	2007	2008	2007
Partner A	27%	0%	31%	0%
Partner B	26%	0%	28%	0%
Partner C	14%	0%	9%	0%
Partner D	12%	33%	11%	20%
Partner E	2%	28%	4%	32%
Partner F	0%	11%	0%	10%
Partner G	3%	10%	3%	14%

For the three months ended June 30, 2008 and 2007, we derived approximately 11% and 50%, respectively, of our revenue from agencies of the United States Government in aggregate, compared to 12% and 55% for the six months ended June 30, 2008 and 2007, respectively. For the first half of 2008, none of our significant partners were agencies of the United States Government while three significant partners accounted for 32%, 14% and 10% of revenue from agencies of the United States Government for the first half of 2007.

Contract receivables from four significant partners comprised approximately 28%, 16%, 13% and 12% of contract receivables at June 30, 2008. Contract receivables from three significant partners comprised approximately 25%, 19% and 11% of contract receivables at December 31, 2007.

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 financial position and outlook for Isis Pharmaceuticals, Inc. as well as our Ibis Biosciences subsidiary and our Regulus joint venture, and the therapeutic and commercial potential of our technologies and products in development. 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, including those statements that are described as Isis' goals and projections. 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, in developing and commercializing systems to identify infectious organisms that are effective and commercially attractive, and in the endeavor of building a business around such products. 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, 2007, which is on file with the U.S. Securities and Exchange Commission, and those identified within this Item entitled "Risk Factors" beginning on page 29 of this Report.

Table of Contents

Overview

We are a leading company in antisense technology exploiting a novel drug discovery platform to create a broad pipeline of first-in-class drugs. Through our highly efficient and prolific drug discovery platform, we can expand our drug pipeline and our partner's drug 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 conduct early development on these drugs to key value inflection points. Because we can discover more drugs than we can develop, our plan is to discover new drugs, outlicense our drugs to partners and build a growing annuity of milestone payments and royalty income. In this way, we maximize the value of the drugs we discover by licensing our drugs to partners at key development points, which allows us to focus on utilizing our antisense technology platform to discover new drugs. At the same time, we benefit from our partner's expertise to develop, commercialize and market our drugs. For example, we partner our drugs with leading pharmaceutical companies, such as Bristol-Myers Squibb Company, Genzyme and Ortho-McNeil, Inc. as well as with smaller satellite companies that have expertise in specific disease areas. In addition to our cutting edge antisense programs, we maintain technology leadership beyond our core areas of focus through collaborations with Alnylam and Regulus, our joint venture created to focus on microRNA therapeutics. We explore the technology beyond antisense with additional opportunities in infectious disease identification through our Ibis subsidiary and in the discovery and development of aminoglycoside and aptamer drugs through our technology partners, Achaogen, Inc. and Archemix, respectively. 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 and vast patent estate of more than 1,500 issued patents. We remain one of the largest patent holders in the U.S., and with our ongoing research and development, our patent portfolio continues to grow. The patents not only protect our key assets—our technology, our drugs, and the Ibis T5000 Biosensor System–they also form the basis for lucrative licensing and partnering arrangements. We have generated more than $116 million from our intellectual property licensing program that helps support our internal drug discovery and development programs.

In addition to the important progress we and our partners made with our second generation drugs in development and the achievements of our Ibis subsidiary in commercializing the Ibis T5000 Biosensor System, to date in 2008, we have completed several transactions that significantly strengthened our financial position. In January 2008, we entered into a strategic alliance with Genzyme in which Genzyme made a $150 million equity investment in our common stock. Subsequently in June 2008, we received an additional $175 million licensing fee from Genzyme when we completed the detailed mipomersen license agreement. Furthermore in January 2008, we and Ibis entered into a strategic alliance with Abbott in which Abbott made a $20 million investment in Ibis by purchasing 10.25% of Ibis' common stock, a subscription right to purchase an additional 8.35% of Ibis' common stock and a call option to acquire Ibis' remaining equity for $175 million to $190 million. Subsequently in June 2008, Abbott exercised its subscription right and invested an additional $20 million to purchase additional equity in Ibis. Additionally, in April 2008, Regulus entered into a strategic partnership with GSK. These partnerships have provided us with an aggregate of approximately $385 million in cash payments to date and the potential to earn over $2.1 billion in milestone payments. We also will share in the future commercial success of the drugs resulting from these partnerships through profit sharing and royalties as well as in the commercial success of Ibis if Abbott acquires Ibis through earn out payments based on Ibis' future cumulative sales. These transactions represent the value that we are realizing from our extensive product pipeline and the successes of our partnering strategy, and provide us with the financial strength to continue to successfully execute our goals.

As evidenced from our recent partnering successes, we continue to benefit from our business strategy that enables us to discover and develop drugs and technologies, nurturing them until the right time to progress them to partners or to satellite companies. This strategy has provided us with the financial strength and the diverse pipeline of drugs that we have today. Looking forward, we expect to grow our pipeline over the remainder of the year by adding two to four new drugs; already we have added the first drug with PCSK9, our development candidate with BMS for which we earned a $2 million milestone payment.

Business Segments

We focus our business on three principal segments:

Drug Discovery and Development Within our primary business segment, we are exploiting a novel drug discovery platform to create a broad pipeline of first-in-class drugs for us and our partners. Our proprietary technology enables us to 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 selecting the best drugs. This efficiency combined with our rational approach to selecting disease targets enables us to build a large and diverse

Table of Contents

portfolio of drugs designed to treat a variety of health conditions. We currently have 18 drugs in development. Our partners are licensed to develop, with our support, 15 of these 18 drugs, which substantially reduces our development costs. We focus our internal drug development programs on drugs to treat cardiovascular, metabolic and inflammatory diseases. Our partners focus on disease areas such as ocular, viral, inflammatory and neurodegenerative diseases, and cancer.

Ibis Biosciences, Inc. Ibis, formerly a wholly owned subsidiary of Isis and now a majority-owned subsidiary of Isis, has developed and is commercializing its biosensor technology, including the Ibis T5000 Biosensor System and assay kits. Ibis' T5000 offers a unique solution for rapid identification and characterization of infectious agents. It can identify virtually all bacteria, viruses and fungi and provide information about drug resistance, virulence and strain type of these pathogens within several hours. Ibis is developing, manufacturing and selling the Ibis T5000 instruments along with the Ibis T5000 assay kits. Currently we are selling research use only kits for many applications. Examples of these kits include influenza surveillance, *Staphylococcus aureus* genotyping and characterization, antibiotic resistance determination and anthrax genotyping. We continue to develop new kits, and as defined through our agreement with Abbott, we are particularly focused on developing those applications that will be of highest commercial value for the clinical diagnostics market.

Much of the development of the Ibis T5000 Biosensor System and related applications has been funded through government contracts and grants. As of June 30, 2008, we had earned $72.9 million in revenue under our government contracts and grants, and we have an additional $7.9 million committed under our existing contracts and grants.

Regulus Therapeutics LLC In September 2007, we and Alnylam established Regulus as a joint venture focused on the discovery, development, and commercialization of microRNA therapeutics. Regulus is addressing therapeutic opportunities that arise from alterations in microRNA expression. Since microRNAs regulate the expression of broad networks of genes and biological pathways, microRNA therapeutics define a new and potentially high-impact strategy to target multiple points on disease pathways.

To date, microRNAs have been implicated in several disease areas, such as cancer, viral infection, metabolic disorders, and inflammatory diseases. Regulus is currently focusing on several of these disease areas, including microRNA therapeutics that target miR-122, an endogenous liver-specific host gene also required for viral infection by hepatitis C virus, or HCV, and metabolics. Regulus is actively exploring additional areas for development of microRNA therapeutics, including cancer, other viral diseases, metabolic disorders and inflammatory diseases.

Recent Events

Cardiovascular Program

- We completed licensing transaction for mipomersen.
- We finalized and announced 2008 mipomersen development plan with Genzyme.
- We reported a preclinical study in *Circulation* showing that mipomersen lowers Lp(a) and oxidized-LDL, independent risk factors for cardiovascular disease.
- We initiated a pivotal quality phase 2 study in heterozygous FH subjects with coronary artery disease.
- We were granted broad patent coverage for antisense compounds targeting apolipoprotein B, U.S. Patent No. 7,407,943 entitled “Antisense modulation of Apolipoprotein B Expression”.

Metabolic Program

- We highlighted our robust diabetes and obesity portfolio with nine presentations and posters at the American Diabetes Association meeting:
  - We presented new preclinical data relating to ISIS 388626, Isis’ drug targeting SGLT2.
  - We presented results from eight research programs on novel targets that offer new mechanisms to address metabolic diseases, including obesity.

Other Partnered Programs

- ATL and Teva reported encouraging Phase 2 results for ATL/TV1102, targeting VLA-4 in patients with multiple sclerosis.
- Our partnered oncology drugs highlighted at the American Society of Clinical Oncology demonstrate the potential of antisense technology to treat multiple cancers.
  - OncoGenex reported encouraging Phase 2 results on OGX-011, targeting clusterin, in patients with hormone refractory prostate cancer.
  - Eli Lilly and Company reported positive Phase 1 clinical trial results for LY2181308, targeting surviving.
- Atlantic Healthcare received U.S. orphan drug designation for alicaforsen for the treatment of pouchitis.
- Altair Therapeutics advanced AIR 645 into Phase 1 studies for the treatment of asthma.

Regulus Therapeutics (microRNA Joint Venture)

- Regulus entered into a strategic alliance with GlaxoSmithKline.

Table of Contents

- Regulus obtained exclusive rights from Stanford University to worldwide patent applications covering methods and compositions for antagonizing miR-181a.
- Regulus was selected as one of the FierceBiotech’s ‘Fierce 15’ for 2008.

Ibis Biosciences

- We received an additional $20 million investment from Abbott for a total of 18.6 percent equity in Ibis, retaining Abbott’s exclusive option to purchase its remaining equity by June 30, 2009.
- Ibis extended government contracts that add to its revenue and fund the expansion of applications of the Ibis T5000 technology.

Table of Contents

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 the appropriateness of judgments and estimates used in allocating revenue and expenses to operating segments; 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.

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, 2007.

Table of Contents

Results of Operations

Revenue

Total revenue for the three and six months ended June 30, 2008 of $33.0 million and $54.3 million, respectively, was significantly higher than the revenue for the same periods in 2007 of $3.8 million and $6.3 million due to the addition of revenue from new collaborations. As part of our strategic relationship with Genzyme, Genzyme purchased $150 million of our common stock at $30 per share and in the second quarter paid us a licensing fee of $175 million. We are amortizing the premium on the stock, $100 million calculated using a Black-Scholes option valuation model, and the licensing fee ratably into revenue until June 2012, which represents the end of our performance obligation based on the research and development plan included in the agreement. In addition to the Genzyme revenue, in the second quarter of 2008, we continued to recognize significant value from our portfolio of antisense drugs and our satellite companies. In the second quarter of 2008, we earned a $2.0 million milestone payment from BMS when it moved PCSK9 into development as well as sublicense revenue of $4.6 million from Alnylam from its transaction with Takeda Pharmaceutical Company Limited and $1.4 million from ATL from its transaction with Teva. Our subsidiaries also contributed to the increase in our 2008 year to date revenue compared to the same period in 2007. In the second quarter of 2008, Regulus began recognizing revenue from its collaboration with GSK while Ibis experienced an 80% growth in its year to date revenues, which is discussed further in the Regulus Therapeutics and Ibis Biosciences, Inc. sections below.

Quarter-to-quarter fluctuations in revenue are common for us as our revenue is significantly affected by the nature and timing of payments under agreements with our partners, including license fees and milestone-related payments, such as the $2 million milestone payment we received from BMS and the $4.6 million and the $1.4 million sublicense fees we earned from Alnylam and ATL, respectively, which are included in revenue in the second quarter of 2008.

The following table sets forth information on our revenue by segment (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2008	2007	2008	2007
Drug Discovery and Development:				
Research and development revenue	$ 22,900	$ 1,591	$ 40,514	$ 2,017
Licensing and royalty revenue	6,147	331	6,815	779
	$ 29,047	$ 1,922	$ 47,329	$ 2,796
Ibis Biosciences:				
Research and development revenue	$ 2,160	$ 1,081	$ 3,944	$ 2,026
Commercial revenue (1)	1,098	810	2,293	1,441
	$ 3,258	$ 1,891	$ 6,237	$ 3,467
Regulus Therapeutics:				
Research and development revenue	$ 656	$ —	$ 748	$ —
	$ 656	$ —	$ 748	$ —
Total Revenue:				
Research and development revenue	$ 25,716	$ 2,672	$ 45,206	$ 4,043
Commercial revenue (1)	1,098	810	2,293	1,441
Licensing and royalty revenue	6,147	331	6,815	779
	$ 32,961	$ 3,813	$ 54,314	$ 6,263

(1) Ibis Biosciences' commercial revenue has been classified as research and development revenue under collaborative agreements on Isis' Condensed Consolidated Statements of Operations.

Drug Discovery & Development

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for the three and six months ended June 30, 2008 was $22.9 million and $40.5 million, respectively, compared to $1.6 million and $2.0 million for the same periods in 2007. The increase is primarily due to revenue from our collaborations with BMS, OMI and Genzyme.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties for the three and six months ended June 30, 2008 was $6.1 million and $6.8 million, respectively, and was higher compared to $331,000 and $779,000 for the same periods in 2007 due to the $4.6 million and $1.4 million of sublicensing revenue we earned from Alnylam and ATL in the second quarter of 2008.

Ibis Biosciences, Inc.

Ibis' revenue for the three and six months ended June 30, 2008 was $3.3 million and $6.2 million, respectively, compared to $1.9 million and $3.5 million for the same periods in 2007. Primarily as a result of the increased number of T5000 Biosensor System placements during fiscal year 2007 compared to 2006, Ibis' commercial revenue of $1.1 million and $2.3 million for the three and six months ended June 30, 2008 was higher than its commercial revenue of $810,000 and $1.4 million for the same periods in 2007. Commercial revenue consisted of revenue from sales of Ibis T5000 Biosensor Systems and assay kits, as well as revenue from Ibis' assay services business. Because Ibis provides a full year of support for each Ibis T5000 Biosensor System following installation, Ibis is amortizing the revenue for instrument and assay kits over the period of this support obligation. In addition, Ibis' commercial revenue included revenue from the distribution agreement Ibis and Abbott entered into in March 2008. Ibis' revenue from government contracts was $2.2 million and $3.9 million for the three and six months ended June 30, 2008, representing an increase over $1.1 million and $2.0 million for the same periods in 2007, driven primarily by contracts awarded in late 2007 and 2008 to date. Ibis was awarded $3.2 million of new contracts in the first half of 2008 that support Ibis' continued revenue growth by expanding the applications for the T5000 Biosensor System.

From inception through June 30, 2008, Ibis has earned $72.9 million in revenue from various government agencies to further the development of our Ibis T5000 Biosensor System and related assay kits. An additional $7.9 million is committed under existing contracts and grants. Ibis may receive additional funding under these contracts based upon a variety of factors, including the accomplishment of program objectives and the exercise of contract options by the contracting agencies. These agencies may terminate these contracts and grants at their convenience at any time, even if we have fully performed our obligations. Consequently, we may never receive the full amount of the potential value of these awards.

Regulus Therapeutics

Regulus' revenue for the three and six months ended June 30, 2008 was $656,000 and $748,000 related primarily to revenue from its collaboration with GSK and to a lesser extent to a Small Business Innovation Research grant from the National Institute of Allergy and Infectious Diseases, a part of the National Institutes of Health, which is funding further research for the miR-122 program. As part of Regulus' strategic alliance with GSK, Regulus received a $15 million upfront fee, which we began amortizing into revenue in the second quarter of 2008 and will continue to amortize over Regulus' six year period of performance under the agreement. Because Regulus was formed in the third quarter of 2007, it did not have revenue in the first half of 2007.

Operating Expenses

Operating expenses for the three and six months ended June 30, 2008 were $36.1 million and $66.3 million, respectively, compared to $23.5 million and $46.8 million for the same periods of 2007. We have expanded our clinical development programs as our drugs advance in development, resulting in an increase in operating expenses of $2.9 million in the first half of 2008 compared to the first half of 2007. Additionally, Ibis' operating expenses have increased by $5.9 million in the first half of 2008 compared to the first half of 2007 to support the growth of its commercial business and the cost of activities to achieve milestones as part of Abbott's investment and purchase option. Also contributing to the increase in operating expenses in the first half of 2008 compared to the first half of 2007 was $4.0 million of expenses associated with our joint venture, Regulus, which are expected to increase over the remainder of the year as Regulus increases its staffing and outside research.

Furthermore, contributing to the increase in operating expenses was an increase in non-cash compensation expense related to stock options. Non-cash compensation expense related to stock options was $4.0 million and $7.8 million for the three and six months ended June 30, 2008 compared to $2.4 million and $4.8 million for the same periods in 2007, primarily reflecting the increase in our stock price from the first half of 2007 to the first half of 2008.

Our operating expenses by segment were as follows (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2008	2007	2008	2007
Drug Discovery and Development	$ 24,897	$ 18,712	$ 46,677	$ 37,353
Ibis Biosciences	8,674	4,761	15,550	9,471
Regulus Therapeutics	2,523	—	4,050	—
Total operating expenses	$ 36,094	$ 23,473	$ 66,277	$ 46,824

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. 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. Also included in research and development expenses are Ibis' and Regulus' research and development expenses. The following table sets forth information on research and development costs (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2008	2007	2008	2007
Research and development expenses	$ 28,004	$ 18,432	$ 51,376	$ 36,455
Non-cash compensation expense related to stock options	3,191	1,952	6,266	3,878
Total research and development expenses	$ 31,195	$ 20,384	$ 57,642	$ 40,333

Our research and development expenses by segment were as follows (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2008	2007	2008	2007
Drug Discovery and Development	$ 22,939	$ 16,658	$ 42,701	$ 32,885
Ibis Biosciences	6,650	3,726	12,023	7,448
Regulus Therapeutics	1,606	—	2,918	—
Total research and development expenses	$ 31,195	$ 20,384	$ 57,642	$ 40,333

For the three and six months ended June 30, 2008, we incurred total research and development expenses, excluding non-cash compensation expense, of $28.0 million and $51.4 million, respectively, compared to $18.4 million and $36.5 million for the same periods in 2007. We attribute the increase to the expansion of our key programs, activities required to commercialize the Ibis T5000 Biosensor System and achieve milestones as part of the Abbott transaction and Regulus' research activities. Expenses related to Ibis and Regulus are discussed in separate sections below.

Drug Discovery & Development

Antisense Drug Discovery

Using proprietary antisense oligonucleotides to identify what a gene does, called gene functionalization, and then determining whether a specific gene is a good target for drug discovery, called target validation, are the first steps in our drug discovery process. 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.

Table of Contents

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.

Antisense drug discovery costs, excluding non-cash compensation expense, for the three and six months ended June 30, 2008 were $4.5 million and $8.7 million, respectively, compared to $3.2 million and $6.6 million for the same periods in 2007. The higher expenses in 2008 compared to 2007 were primarily due to increased activity levels related to our planned investment to fill our pipeline and additional spending to support collaborative research efforts, which required an increase in personnel and lab supplies.

Antisense Drug Development

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2008	2007	2008	2007
Mipomersen	$ 3,070	$ 2,482	$ 6,581	$ 4,222
Other antisense development projects	4,035	3,055	6,790	5,656
Development overhead costs	840	988	1,747	2,327
Non-cash compensation expense related to stock options	860	689	1,778	1,340
Total antisense drug development	$ 8,805	$ 7,214	$ 16,896	$ 13,545

Antisense drug development expenditures were $7.9 million and $15.1 million, excluding non-cash compensation expense related to stock options, for the three and six months ended June 30, 2008 compared to $6.5 million and $12.2 million for the same periods in 2007. We attribute the increase primarily to the continued development of mipomersen, including the Phase 3 program, and increases in our metabolic disease development projects. Development overhead costs were $840,000 and $1.7 million for the three and six months ended June 30, 2008, compared to $988,000 and $2.3 million for the same periods in 2007. The decrease in overhead costs was primarily a result of people shifting the hours they worked from non-project specific activities to specific projects related to the development of our drugs. We expect our drug development expenses to fluctuate based on the timing and size of our clinical trials.

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 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, 15 of our 18 drug candidates, which substantially reduces our development costs. As part of our collaboration with Genzyme, we will over time transition the development responsibility to Genzyme and Genzyme will be responsible for the commercialization of mipomersen. We will contribute 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. Manufacturing and operations expenses, excluding non-cash compensation expense, for the three and six months ended June 30, 2008 were $2.8 million and

Table of Contents

$5.4 million, respectively, compared to $1.5 million and $3.0 million for the same periods in 2007. 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. The increase is primarily due to the costs associated with the manufacturing of drug supplies for our corporate partners and to support our expanded internal drug development programs.

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 June 30,		Six Months Ended June 30,	
	2008	2007	2008	2007
Personnel costs	$ 1,395	$ 1,468	$ 2,867	$ 3,004
Occupancy	1,596	1,463	3,098	2,977
Depreciation and amortization	1,564	1,186	2,684	2,392
Insurance	206	250	452	487
Other	1,298	327	1,036	914
Non-cash compensation expense related to stock options	574	189	1,215	370
Total R&D support costs	$ 6,633	$ 4,883	$ 11,352	$ 10,144

R&D support costs, excluding non-cash compensation expense related to stock options, for the three and six months ended June 30, 2008 were $6.1 million and $10.1 million, respectively, compared to $4.7 million and $9.8 million for the same periods in 2007. The slight increase in the first half of 2008 compared to the first half of 2007 is primarily a result of the increase in additional expenses to support the continued development of our key programs and an increase in amortization associated with a non-cash charge for patents assigned to certain of our partners, offset by the $750,000 we received from Ercole in March 2008 as repayment of a convertible note that we had previously expensed.

Our R&D support costs by segment were as follows (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2008	2007	2008	2007
Drug Discovery and Development	$ 5,890	$ 4,209	$ 9,900	$ 8,745
Ibis Biosciences	743	674	1,452	1,399
Total R&D support costs	$ 6,633	$ 4,883	$ 11,352	$ 10,144

Selling, General and Administrative Expenses

Selling, 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 business development, legal, human resources, investor relations, finance, Ibis' selling, general and administrative and Regulus' general and administrative expenses, which began in September 2007 when Regulus was formed. Additionally, we include in selling, 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. Until the acquisition of Symphony GenIsis in September 2007, selling, general and administrative expenses also included Symphony GenIsis' general and administrative expenses.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2008	2007	2008	2007
Selling, general and administrative expenses	$ 4,084	$ 2,652	$ 7,137	$ 5,616
Non-cash compensation expense related to stock options	815	437	1,498	875
Total selling, general and administrative expenses	$ 4,899	$ 3,089	$ 8,635	$ 6,491

Table of Contents

Our selling, general and administrative expenses by segment were as follows (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2008	2007	2008	2007
Drug Discovery and Development	$ 1,958	$ 2,054	$ 3,976	$ 4,468
Ibis Biosciences	2,024	1,035	3,527	2,023
Regulus Therapeutics	917	—	1,132	—
Total selling, general and administrative expenses	$ 4,899	$ 3,089	$ 8,635	$ 6,491

Selling, general and administrative expenses, excluding non-cash compensation expense related to stock options, for the three and six months ended June 30, 2008 were $4.1 million and $7.1 million, respectively, compared to $2.7 million and $5.6 million for the same periods in 2007. The increase is primarily due to additional sales and customer support costs to maintain the commercial growth of the Ibis T5000 Biosensor System and expenses related to Regulus. Expenses related to Ibis and Regulus are discussed in separate sections below.

Ibis Biosciences, Inc.

Ibis' operating expenses include cost of goods sold for its commercial activities, research and development expenses and selling, general and administrative expenses. Ibis' cost of goods sold is primarily the result of its performance under government contracts in support of the ongoing development of the Ibis T5000 Biosensor System and related assay kits. Ibis' cost of goods sold includes all contract-related costs it incurs on behalf of government agencies in connection with the performance of its obligations under the respective contracts, including costs for equipment to which the government retains title. Research and development expenditures in Ibis include costs for scientists, laboratory supplies, chemicals and highly specialized consultants to advance the research and development of the Ibis T5000 Biosensor System. Further, we allocate a portion of R&D support costs to Ibis and include this allocation in Ibis' research and development expenses. Ibis' selling, general and administrative expenses include outside costs in the areas of business development, customer support, human resources, and finance. In addition, we allocate a portion of corporate expenses required to support Ibis to Ibis' selling, general and administrative expenses.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2008	2007	2008	2007
Cost of goods sold	$ 3,078	$ 1,266	$ 3,895	$ 2,801
Research and development costs	3,247	2,156	7,443	4,043
Selling, general and administrative expenses	1,883	933	3,270	1,812
Non-cash compensation expense related to stock options	466	406	942	815
Total Ibis operating expenses	$ 8,674	$ 4,761	$ 15,550	$ 9,471

Ibis' operating expenses, excluding non-cash compensation expense related to stock options, were $8.2 million and $14.6 million for the three and six months ended June 30, 2008, compared to $4.4 million and $8.7 million for the same periods in 2007, respectively. The increase in operating expenses primarily reflects an increase in costs to support the growth of Ibis' commercial business including selling and support costs for the Ibis T5000 Biosensor System and the cost to achieve milestones as part of the Abbott transaction. We expect costs and expenses for Ibis to increase as we continue to expand this business.

Regulus Therapeutics

In September 2007, we and Alnylam formed Regulus, a joint venture focused on the discovery, development, and commercialization of microRNA therapeutics. Under accounting rules, we are considered the primary beneficiary of Regulus and consolidate the financial results of Regulus. As a result, our condensed consolidated financial statements include a line item called "Noncontrolling Interest in Regulus Therapeutics LLC." On our Condensed Consolidated Balance Sheet, this line reflects Alnylam's minority ownership of Regulus' equity. As the joint venture progresses, this line item will be reduced by Alnylam's share of Regulus' net losses, which were $1.8 million for the first half of 2008 until the balance becomes zero. The reductions to the Noncontrolling Interest in Regulus will be reflected in our Condensed Consolidated Statement of Operations using a similar line item and will provide a positive adjustment to our net loss equal to Alnylam's share of Regulus' losses. With the recently announced strategic alliance with GSK, we anticipate Regulus' expenses to increase as Regulus continues to advance its research and development activities, consisting primarily of increases to its staffing levels and outside research activities to achieve the milestones under this collaboration.

Table of Contents

Investment Income

Investment income for the three and six months ended June 30, 2008 totaled $560,000 and $5.5 million, respectively, compared to $3.1 million and $6.5 million for the same periods in 2007. The decrease in investment income was primarily due to the lower average returns on our investments resulting from the condition of the financial markets. Included in investment income for 2008 are non-cash adjustments related to value of the call option and subscription right that we granted to Abbott. The non-cash adjustments reduced investment income for the second quarter of 2008 by $1.7 million and increased investment income for the first half of 2008 by $179,000. Excluding these non-cash adjustments, interest income would have been $2.3 million and $5.3 million for the three and six months ended June 30, 2008. We anticipate interest income, without non-cash adjustments, to be higher in future quarters due to a higher average cash balance because we received the $175 million license fee from Genzyme and the $20 million investment in Ibis from Abbott at the end of June 2008.

Interest Expense

Interest expense for the three and six months ended June 30, 2008 totaled $1.4 million and $2.8 million, respectively, compared to $2.0 million and $4.6 million for the same periods in 2007. The decrease in interest expense was due to the effect of a lower average debt balance in the first half of 2008 compared to the first half of 2007 primarily related to the fact that a portion of our old $5^1/_2$% notes was outstanding until we repaid the remaining balance in May 2007.

Gain on Investments

Gain on investments for the three and six months ended June 30, 2007 was $2.0 million and $3.5 million, respectively, reflecting a gain realized on the sale of the remaining equity securities of Alnylam that we owned. We did not recognize any gain on investments for the first half of 2008.

Loss on Early Retirement of Debt

Loss on early retirement of debt for the three and six months ended June 30, 2007 was $2.0 million and $3.2 million, respectively, reflecting the early extinguishment of our $5^1/_2$% convertible subordinated notes in the first half of 2007. We did not recognize any loss on early retirement of debt for the first half of 2008.

Net Loss Applicable to Common Stock

Net loss applicable to common stock for the three and six months ended June 30, 2008 was $2.2 million and $6.5 million, respectively, compared to $11.0 million and $24.0 million for the same periods in 2007. Our net loss for the first half of 2008 was significantly lower than the first half of 2007 primarily due to the decrease in our loss from operations and interest expense, offset by the $14.4 million loss attributed to the noncontrolling interest in Symphony GenIsis, Inc. that we recorded in the first half of 2007. We did not record this benefit in the first half of 2008 because we purchased all of the equity of Symphony GenIsis in the third quarter of 2007, saving $75 million in the predetermined purchase price. Also contributing to the decrease in our net loss was the noncontrolling interest that we recorded in 2008 for Regulus ($1.8 million) and Ibis ($896,000).

Net Loss Per Share

Net loss per share for the three and six months ended June 30, 2008 was $0.02 per share and $0.07 per share, respectively, compared to $0.13 per share and $0.29 per share for the same periods in 2007. The decrease in net loss per share for the first half of 2008 compared to the first half of 2007 was primarily a result of the decrease in net loss applicable to common stock discussed above.

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. From our inception through June 30, 2008, we have earned approximately $631.6 million in revenue from contract research and development, the sale and licensing of our intellectual property and commercial revenue from sales of Ibis T5000 Biosensor Systems and assay kits, as well as revenue from Ibis' assay services business. From the time we were founded through June 30, 2008, we have raised net proceeds of approximately $794.9 million from the sale of our equity securities and we have borrowed approximately $548.8 million under long-term debt arrangements to finance a portion of our operations.

Table of Contents

At June 30, 2008, we had cash, cash equivalents and short-term investments of $537.0 million and stockholders' equity of $59.0 million. In comparison, we had cash, cash equivalents and short-term investments of $193.7 million and stockholders' equity of $872,000 as of December 31, 2007. As of June 30, 2008, we had consolidated working capital of $428.1 million compared to $145.1 million at December 31, 2007. The cash we received in the first half of 2008 from Genzyme ($325.0 million), Abbott ($40.5 million) and GSK ($20.0 million) primarily led to the increase in our consolidated working capital offset by $68.9 million of deferred revenue from Genzyme and GSK that is included in current liabilities.

As of June 30, 2008, our debt and other long-term obligations totaled $171.6 million, compared to $170.1 million at December 31, 2007. The increase in our debt and other obligations was due to the $5 million convertible promissory note Regulus issued to GSK partly offset by the declining balance on our Silicon Valley Bank term loan. We will continue to use equipment lease financing as long as the terms remain commercially attractive.

Based on our existing and committed cash, not including the $175 million to $190 million we could receive from Abbott if Abbott completes its purchase of Ibis in 2008, we expect that our 2008 year end cash balance will be greater than $450 million and will last for at least five years.

The following table summarizes our contractual obligations as of June 30, 2008. The table provides a breakdown of when obligations become due. A more detailed description of the major components of our debt is provided 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**
$2^5/_8$% Convertible Subordinated Notes	$ 162.5	$ —	$ —	$ —	$ 162.5

GSK Convertible Promissory Note	$	5.0	$	—	$	5.0	$	—	$	—
Silicon Valley Bank Term Loan	$	3.7	$	3.7	$	—	$	—	$	—
Other Obligations	$	0.4	$	—	$	—	$	—	$	0.4
Operating Leases	$	20.5	$	3.5	$	5.9	$	2.8	$	8.3

Our contractual obligations consist primarily of our publicly traded convertible debt. In addition, we also have a convertible promissory note from GSK, a term loan from Silicon Valley Bank and other obligations.

In December 2003, we secured a $32.0 million term loan from Silicon Valley Bank to retire debt from two partners. We are amortizing the term loan over sixty months. The term loan requires monthly payments of principal plus accrued interest, and bears interest at the prime interest rate less applicable discounts based on the balances in the cash and investment accounts that we maintain at Silicon Valley Bank, which was 4.25% at June 30, 2008. The loan is secured by substantially all of our operating assets, excluding intellectual property, real estate, and certain equity investments. The loan is subject to certain liquidity requirements, including a requirement that we maintain a minimum balance in an account at Silicon Valley Bank at all times equal to the outstanding balance of the loan. The loan is convertible to a fixed interest rate at our option at any time at the then-applicable prime rate plus 1.25%. The carrying value of the term loan at June 30, 2008 was $3.7 million, which we expect to fully repay by December 31, 2008 according to the loan's terms.

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. The $162.5 million convertible subordinated notes bear interest at $2^5/_8$%, which is payable semi-annually, and mature in 2027. The $2^5/_8$% notes are convertible, at the option of the note holders, into approximately 11.1 million shares of 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% of the principal amount between February 15, 2012 and February 14, 2013; 100.375% of the principal amount between February 15, 2013 and February 14, 2014; and 100% of the principal amount thereafter. Holders of the $2^5/_8$% notes are also able to require us to repurchase the $2^5/_8$% notes on February 15, 2014, February 15, 2017 and February 15, 2022, and upon the occurrence of certain defined conditions, at 100% of the principal amount of the $2^5/_8$% notes being repurchased plus accrued interest and unpaid interest. Using the net proceeds from the issuance of our $2^5/_8$% notes, we repaid the entire $125 million of our $5^1/_2$% convertible subordinated notes due 2009.

In connection with the strategic alliance with GSK in April 2008, Regulus issued a convertible promissory note to GSK in exchange for $5 million in cash. The convertible note bears interest at the prime rate, which was 5.00% at June 30, 2008. The note plus interest will convert into Regulus common 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 is not repaid in cash after three years, we, Alnylam and Regulus may elect to repay the note plus interest with shares of each company's common stock.

Table of Contents

In addition to contractual obligations, we had outstanding purchase orders as of June 30, 2008 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. In addition to the other information in this report on Form 10-Q, you should carefully consider the risks described below before purchasing our securities. 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, 2007.

Risks Associated with our Businesses as a Whole

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

Because product discovery and development require substantial lead-time and money prior to commercialization, our expenses have exceeded our revenue since we were founded in January 1989. As of June 30, 2008, we had accumulated losses of approximately $834.2 million and stockholders' equity of approximately $59.0 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from selling, 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 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.

Many of the drugs in our development pipeline are being developed and/or funded by corporate partners, including Altair Therapeutics Inc., Antisense Therapeutics Limited, Atlantic Healthcare (UK) Limited, BMS, iCo Therapeutics Inc., ImQuest Pharmaceuticals, Inc., Eli Lilly and Company,

Merck & Co., Inc., OncoGenex Technologies Inc. and OMI. In addition, in January 2008 we entered 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, Lilly discontinued its investment in Affinitak.

Table of Contents

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.

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, OMI and BMS, 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, OMI, or BMS, 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 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.

In addition, our Ibis business relies in part on trade secret laws and nondisclosure, confidentiality and other agreements to protect some of the proprietary technology that is part of the Ibis T5000 Biosensor System. However, these laws and agreements may not be enforceable or may not provide meaningful protection for Ibis' trade secrets or other proprietary information in the event of unauthorized use or disclosure or other breaches of these agreements.

Until recently, virtually all of Ibis' research and development activities have been funded under contracts from the U.S. government (either directly or through subcontracts from prime contractors or higher-tier subcontractors). As a general matter, subject to certain disclosure, notice, filing, acknowledgement and reporting obligations, Ibis is entitled to retain title to any inventions conceived or first reduced to practice under government contracts, but the government will have a nonexclusive, nontransferable, irrevocable, paid-up license to practice or have practiced these inventions for or on behalf of the United States.

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.

Table of Contents

For example, in December 2006, the European Patent Office (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. 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. Based on our existing and committed cash, not including the $175 million to $190 million we could receive from Abbott if Abbott completes its purchase of Ibis in 2008, we expect that our 2008 year end cash balance will be greater than $450 million and will last for at least five years. 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;
- success in developing and commercializing a business based on our Ibis T5000 Biosensor System to identify infectious organisms; 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.

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.

Table of Contents

For example, in April 2008 the FDA provided guidance regarding approval requirements for mipomersen. The FDA indicated that reduction of LDL-cholesterol 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 2010. 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 to accelerate our planned outcome trial.

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.

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 June 30, 2008, the market price of our common stock ranged from $9.52 to $20.15 per share. 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 such 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 we cannot be certain that the coverage or coverage limits of our insurance policies will be adequate. In the event our losses exceed our insurance coverage, our financial condition would be adversely affected.

Table of Contents

If a natural or man-made disaster strikes our research and development facilities, it could delay our progress developing and commercializing our drugs or our Ibis T5000 Biosensor System.

We are developing our Ibis T5000 Biosensor System in our facility located in Carlsbad, California. Additionally, we manufacture our research and clinical supplies in a separate manufacturing facility located in Carlsbad, California. The facilities and the equipment we use to develop the Ibis T5000 Biosensor System and manufacture our drugs would be costly to replace and could require substantial lead time to repair or replace. Either of 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% of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15% 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.

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 12,000,000 shares of our common stock and 2,999,998 shares of our common stock issuable upon the exercise of the warrants we issued as part of our August 2005 private placement as well as 4.25 million shares of our common stock issuable upon the exercise of the warrant we issued to Symphony GenIsis Holdings. In addition, on December 22, 2005, we filed a Form S-3 shelf registration statement with the SEC to register up to $200,000,000 worth of our common stock for possible issuance. Finally, we have registered for resale our $2^{5}/_{8}$% convertible subordinated notes, including the approximately 11,111,116 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.

Table of Contents

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 (PCAOB) or the Nasdaq Global Market. Any such action could adversely affect our financial results and the market price of our common stock.

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.

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 non-small cell lung cancer 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 an NDA 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;

Table of Contents

- 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 profitable.

Our success will depend upon the medical community, patients and third-party payors accepting our products as medically useful, cost-effective and safe. We cannot guarantee that, if approved for commercialization, doctors will use our products to treat patients. We currently have one commercially approved drug product, Vitravene, a treatment for cytomegalovirus, or 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;
- 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 or result in FDA enforcement action after approval that could limit the commercial success of our potential products.

Table of Contents

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; or
- more effective 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.

Regulus is our joint venture with Alnylam focused 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 managing board comprised of an equal number of directors appointed by each of Alnylam and us. Regulus researches and develops microRNA projects and programs pursuant to an operating plan that is approved by the managing board. Any disagreements between Alnylam and us regarding a

development decision or any other decision submitted to Regulus' managing 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 each of our clinical trials is conducted 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 Ibis Biosciences Business

We may not successfully develop or derive revenues from our business based on our Ibis T5000 Biosensor System.

Our Ibis T5000 Biosensor System is subject to the risks inherent in developing tools based on innovative technologies. Our product is at an early stage of development and requires continued research and development to achieve

Table of Contents

our business objectives. For Ibis to be commercially successful, we must convince potential customers that our Ibis T5000 Biosensor System is an attractive alternative to existing methods of identifying pathogens. If our potential customers fail to purchase our Ibis T5000 Biosensor System due to competition or other factors, or if we fail to develop applications that lead to market acceptance, we may not recover our investment in this technology and our Ibis T5000 Biosensor System business could fail to meet our business and financial objectives.

If we fail to sell the Ibis T5000 Biosensor System to a minimum customer base, our ability to generate revenues from sales of assay kits will be negatively affected.

A key element of our business plan for Ibis calls for us to deploy the Ibis T5000 Biosensor System to a broad customer base. If we cannot create a broad installed base of our Ibis T5000 Biosensor System, our ability to sell assay kits, the consumables used to operate the system, may be significantly and adversely affected. Even if we successfully achieve broad installation of the Ibis T5000 Biosensor System, customers may not perform as many analyses as we anticipate, which may affect the assumptions underlying our business plan for Ibis and lead to lower-than-expected revenues.

We will depend on Bruker Daltonics to manufacture the Ibis T5000 Biosensor System and any failure of Bruker Daltonics to fulfill its obligations could harm or delay our commercialization efforts.*

In July 2006, we entered into a strategic alliance with Bruker Daltonics to manufacture and distribute the Ibis T5000 Biosensor System. Bruker Daltonics will be the exclusive, worldwide manufacturer of the Ibis T5000 Biosensor System and will also be responsible for order processing, system installations and service in North America, Europe and the Middle East. In Europe and the Middle East, Bruker Daltonics will have exclusive rights to sell Ibis T5000 Biosensor Systems and Ibis assay kits for various government applications, and non-exclusive rights to sell to customers for all other applications except diagnostics. As such, we rely heavily on Bruker Daltonics to successfully manufacture, distribute and service our Ibis T5000 Biosensor System, but do not control many aspects of Bruker Daltonics activities. We believe Bruker Daltonics has failed to satisfactorily perform its obligations under the agreement. We have an active dispute with Bruker regarding its performance under the agreement. If Bruker Daltonics continues to fail to carry out its obligations under our alliance, its failure could harm or delay the commercialization of our Ibis T5000 Biosensor System.

Ibis' strategic alliance with Abbott may restrict the way Ibis conducts its business and may not result in the ultimate sale of Ibis to Abbott.

On January 30, 2008, we and Ibis entered into a Strategic Alliance Master Agreement with Abbott. As part of this transaction, we granted Abbott an exclusive option to acquire from us all remaining Ibis capital stock. Under the exclusive option, we and Ibis must obtain Abbott's consent before we or Ibis can take specified actions, such as amending Ibis' certificate of incorporation, redeeming, repurchasing or paying dividends on Ibis capital stock, issuing any Ibis capital stock, entering into a transaction for the merger, consolidation or sale of Ibis, creating any Ibis indebtedness, or entering into any Ibis strategic alliance, joint venture or joint marketing agreement. These consent requirements may restrict the way Ibis conducts its business and may discourage others from trying to collaborate with or buy our Ibis subsidiary. Abbott's decision to exercise the exclusive option is at its sole discretion. As a result, we cannot guarantee that Abbott will exercise its option to acquire the remaining Ibis capital stock. If Abbott does not exercise its option to acquire the remaining Ibis capital stock, we will not realize the full benefit of the strategic alliance and we may need to secure a new partner to further expand the Ibis business into the areas of hospital associated infection control and infectious disease diagnostics.

We depend on government contracts for most of Ibis' revenues and the loss of government contracts or a decline in funding of existing or future government contracts could adversely affect our revenues and cash flows.

Historically, most of Ibis' revenues were from the sale of services and products to the U.S. government. The U.S. government may cancel these contracts at any time without penalty or may change its requirements, programs or contract budget or decline to exercise option periods, even if we have fully performed our obligations. Since a large portion of Ibis' government contracts are milestone based, if Ibis fails to meet a specific milestone within the specified delivery date, our government partner may be more likely to reduce or cancel its contract with Ibis. Our revenues and cash flows from U.S. government contracts could also be reduced by declines in U.S. defense, homeland security and other federal agency budgets.

For the six months ended June 30, 2008 and 2007, we derived approximately 12% and 55%, respectively, of our revenue from agencies of the U.S. government. Because of the concentration of our contracts, we are vulnerable to adverse changes in our revenues and cash flows if a significant number of our U.S. government contracts and subcontracts are simultaneously delayed or canceled for budgetary, performance or other reasons.

Table of Contents

If U.S. defense and other federal agencies choose to reduce their purchases under our contracts, exercise their right to terminate contracts, fail to exercise options to renew contracts or limit our ability to obtain new contract awards, our revenues and cash flows could be adversely affected.

We may be liable for penalties under a variety of procurement rules and regulations, and changes in government regulations could adversely impact our revenues, operating expenses and operating margins.

Under our agreements with the U.S. government, we must comply with and are affected by various government regulations that impact our operating costs, operating margins and our internal organization and operation of our businesses. These regulations affect how our customers and we do business and, in some instances, impose added costs on our businesses. Any changes in applicable laws could adversely affect the financial performance of Ibis. With respect to U.S. government contracts, any failure to comply with applicable laws could result in contract termination, price or fee reductions or suspension or debarment from contracting with the U.S. government. Among the most significant regulations are the following:

- the U.S. Federal Acquisition Regulations, which comprehensively regulate the formation, administration and performance of government contracts;
- the U.S. Truth in Negotiations Act, which requires certification and disclosure of all cost and pricing data in connection with contract negotiations; and
- the U.S. Cost Accounting Standards, which impose accounting requirements that govern our right to reimbursement under certain cost-based government contracts.

If our Ibis T5000 Biosensor System's reliability does not meet market expectations, we may be unable to retain our existing customers and attract new customers.

Complex instruments such as our Ibis T5000 Biosensor System typically require operating and reliability improvements following their initial introduction. As we continue to develop our Ibis T5000 Biosensor System and its related applications, we will need to make sure our customers are satisfied with the sensor's reliability. Our efforts to satisfy our customer's needs for instrument reliability could result in greater than anticipated service expenses or divert other resources. Additionally, if we fail to resolve reliability issues as they develop, we could materially damage our reputation, which could prevent us from retaining our existing customers and attracting new customers.

If we had to replace a supplier of one of the major hardware components of our Ibis T5000 Biosensor System, it could delay our commercialization efforts and lengthen our sales cycle.

We have a single supplier for each major hardware component of our Ibis T5000 Biosensor System. Although, we believe we would be able to find a replacement provider, if any of these suppliers stopped providing us with their respective components, identifying and securing a suitable replacement could delay our commercialization efforts and lengthen our sales cycle. For example, Bruker Daltonics supplies the mass spectrometer we use as part of our Ibis T5000 Biosensor System.

If Ibis fails to compete effectively, it may not succeed or contribute significant revenues.

The market for products such as Ibis' is highly competitive. Currently, large reference laboratories, public health laboratories and hospitals perform the majority of diagnostic tests used by physicians and other health care providers. We expect that these laboratories will compete vigorously to maintain their dominance in the diagnostic testing market. To remain competitive, we will need to continually improve Ibis' products so that, when compared to alternatives, its products:

- provide faster results;
- are cost-effective;
- deliver more accurate information;
- are more user friendly; and

Table of Contents

- support a broad range of applications.

If Ibis cannot keep its products ahead of its competitors in these areas, Ibis' revenues will suffer and we may not meet our commercialization goals.

Many of Ibis' competitors have, and in the future these and other competitors may have, significantly greater financial, marketing, sales, manufacturing, distribution and technological resources than Ibis. Moreover, these companies may have substantially greater expertise in conducting clinical trials and research and development, greater ability to obtain necessary intellectual property licenses and greater brand recognition than Ibis. In addition, Ibis' competitors may be in a better position to respond quickly to new or emerging technologies, may be able to undertake more extensive marketing campaigns, may adopt more aggressive pricing policies and may be more successful in attracting potential customers, employees and strategic partners than Ibis.

Improvements in preventing major diseases could reduce the need for our Ibis T5000 Biosensor System and related assay kits, which in turn could reduce our revenues.

We expect to derive a significant portion of our Ibis revenues from the sale of assay kits necessary to use our Ibis T5000 Biosensor System. The need to quickly identify and contain major threats, such as the avian flu, could increase the demand for our assay kits. Conversely, improvements in containing or treating a threat, such as vaccines, would significantly reduce the need to identify and contain the threat. Any reduction in the need to identify or contain a threat could diminish the need for our assay kits, which could reduce our revenues.

Our plans to commercialize the Ibis T5000 Biosensor System internationally are subject to additional risks that could negatively affect our operating results.

Our success will depend in part on our ability and Bruker Daltonics' ability to market and sell the Ibis T5000 Biosensor System and assay kits in foreign markets. Expanding our international operations could impose substantial burdens on our resources, divert management's attention from domestic operations and otherwise adversely affect our business. Furthermore, international operations are subject to several inherent risks including:

- trade protective measures and import or export licensing requirements or other restrictive actions by U.S. and foreign governments could prevent or limit our international sales;
- reduced protection of intellectual property rights;
- changes in foreign currency exchange rates;
- changes in specific country's or region's political or economic conditions; and
- changes in tax laws.

If we cannot access or license rights to particular nucleic acid sequences for targeted diseases in the future, we may be limited in our ability to develop new products and access new markets.

Although our research staff seeks to discover particular nucleic acid sequences for targeted diseases, our ability to offer diagnostic tests for diseases may depend on the ability of third parties to discover particular sequences or markers and correlate them with disease, as well as the rate at which such discoveries are made. Our ability to design products that target these diseases may depend on our ability to obtain the necessary access to raw materials or intellectual property rights from third parties who make any of these discoveries. If we are unable to access new technologies or the rights to particular sequences or markers necessary for additional diagnostic products on commercially reasonable terms or at all, we may not be able to develop new diagnostic products or enter new markets.

The sales cycles for our Ibis T5000 Biosensor Systems are lengthy, and we may expend substantial funds and management effort with no assurance of successfully selling our Ibis T5000 Biosensor Systems or services.

The sales cycles for Ibis T5000 Biosensor Systems are typically lengthy. Our sales and licensing efforts, and those of our partners, will require the effective demonstration of the benefits, value, and differentiation and validation of our products and services, and significant training of multiple personnel and departments within a potential customer organization. We or our partners may be required to negotiate agreements containing terms unique to each prospective

Table of Contents

customer or licensee, which would lengthen the sales cycle. We may expend substantial funds and management effort with no assurance that we will sell our products. In addition, this lengthy sales cycle makes it more difficult for us to accurately forecast revenue in future periods and may cause revenues and operating results to vary significantly in future periods.

If we or our partners are required to obtain regulatory approval for our Ibis T5000 Biosensor System, we may not successfully obtain approval.

Ibis' business plan assumes a significant portion of its revenues will come from Ibis T5000 Biosensor Systems and assay kits for *in vitro* diagnostic purposes, whose uses are regulated by the FDA and comparable agencies of other countries. In addition, customers may wish to utilize the Ibis T5000 Biosensor System and assay kits in manners that require additional regulatory approval. To access these markets, Ibis' products may require either premarket approval or 510(k) clearance from the FDA and other regulatory agencies prior to marketing. The 510(k) clearance process usually takes from three to twelve months from submission, but can take longer. The premarket approval process is much more costly, lengthy, and uncertain and generally takes from six months to two years or longer from submission. In addition, commercialization of any diagnostic or other product that our licensees or collaborators or we develop would depend upon successful completion of preclinical testing and clinical trials. Preclinical testing and clinical trials are long, expensive and uncertain processes, and we do not know whether we, our licensees or any of our collaborators, would be permitted or able to undertake clinical trials of any potential products. It may take us or our licensees or collaborators many years to complete any such testing, and failure could occur at any stage. Preliminary results of clinical trials do not necessarily predict final results, and acceptable results in early clinical trials may not be repeated in later clinical trials. We or our collaborators may encounter delays or rejections of potential products based on changes in regulatory policy for product approval during the period of product development and regulatory agency review. If our Ibis T5000 Biosensor System is considered a medical device, after gaining market approval from the FDA, our Ibis T5000 Biosensor System may be subject to ongoing FDA requirements governing the labeling, packaging, storage, advertising, promotion, recordkeeping and reporting of safety and other post-market information.

If we become subject to product liability claims relating to Ibis, we may be required to pay damages that exceed our insurance coverage.

Any product liability claim brought against us with respect to Ibis, with or without merit, could result in the increase of our product liability insurance rates or the inability to secure coverage in the future. Expenses incurred by our insurance provider in defending these claims will reduce funds available to settle claims or pay adverse judgments. In addition, we could be liable for amounts in excess of policy limits, which would have to be paid out of our cash reserves, and our cash reserves may be insufficient to satisfy the liability. Finally, even a meritless or unsuccessful product liability claim could harm Ibis' reputation in the industry, lead to significant legal fees, and could result in the diversion of management's attention from managing our business.

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.

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 June 30, 2008. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to June 30, 2008.

Table of Contents

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 our agreement with them. We have 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 have failed to achieve resolution of this dispute. Litigation has been filed in Massachusetts Superior Court.

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

Not applicable

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable

Table of Contents

ITEM 4. SUBMISSION OF MATTERS TO A VOTE OF SECURITY HOLDERS

On June 5, 2008, we held our Annual Meeting of Stockholders in Carlsbad, California for the following purposes:

(1) To elect three directors to serve as Class II directors of the Company until the 2011 Annual Meeting of Stockholders. For Director number one, Spencer R. Berthelsen, the number of votes for and withheld was 81,587,555 and 3,674,286, respectively. For Director number two, B. Lynne Parshall, the number of votes for and withheld was 82,603,258 and 2,658,583, respectively. For Director number three, Joseph H. Wender, the number of votes for and withheld was 83,200,118 and 2,061,723, respectively.

(2) To approve an amendment of the 2002 Non-Employee Directors' Stock Option Plan to (i) increase the annual non-discretionary stock option grant for our non-employee directors from 12,500 shares to 15,000 shares and (ii) increase the initial stock option grant from 20,000 shares to 30,000 shares. The number of votes for, against and abstaining was 54,805,810; 3,321,795 and 84,461, respectively.

(3) To approve an increase in shares reserved for issuance under the 1989 Stock Option Plan from 13,200,000 shares to 16,700,000 shares. The number of votes for, against and abstaining was 52,325,673; 3,477,925 and 2,408,468, respectively.

(4) To ratify the appointment of Ernst & Young LLP as the Company's independent registered public accounting firm for the

fiscal year ending December 31, 2008. The number of votes for, against and abstaining was 83,901,707; 1,171,111 and 189,023, respectively.

ITEM 5. OTHER INFORMATION

Not applicable

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.1	License and Co-Development Agreement between the Registrant and Genzyme Corporation dated June 24, 2008 (with certain confidential information deleted).
10.2	Product Development and Commercialization Agreement between Regulus Therapeutics LLC and Glaxo Group Limited dated April 17, 2008 (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.

Table of Contents

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)	August 7, 2008
/s/ B. Lynne Parshall B. Lynne Parshall, J.D.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	August 7, 2008

Exhibit 10.1

LICENSE AND CO-DEVELOPMENT AGREEMENT

BY AND BETWEEN

GENZYME CORPORATION

AND

ISIS PHARMACEUTICALS, INC.

June 24, 2008

TABLE OF CONTENTS

Schedules and Exhibits

LICENSE AND CO-DEVELOPMENT AGREEMENT

This License and Co-Development Agreement (together with all Exhibits, Schedules and other attachments hereto, this "Agreement"), is dated as of the 24th day of June, 2008 (the "Execution Date"), by and between Genzyme Corporation, a Massachusetts corporation ("Genzyme") and Isis Pharmaceuticals, Inc., a Delaware corporation ("Isis"). Genzyme and Isis each may be referred to herein individually as a "Party" or collectively as the "Parties."

WITNESSETH:

WHEREAS, the Parties entered into a License and Research Agreement dated January 7, 2008 and effective as of January 30, 2008 (the "Prior Agreement") pursuant to which Isis granted to Genzyme an exclusive license to certain Isis intellectual property to advance mipomersen, formerly known as ISIS 301012, and related compounds targeting apoB, through human clinical trials and ultimately commercialize it as a product;

WHEREAS, pursuant to Section 2.1.2 of the Prior Agreement, the Parties agreed to negotiate and enter into a more detailed written license and co-development agreement containing additional terms and conditions that are reasonable and customary for license and co-development agreements of this type (the "More Detailed Product Agreement"); and

WHEREAS, the Parties desire to enter into this Agreement to supersede and replace the Prior Agreement and evidence the More Detailed Product Agreement.

NOW, THEREFORE, in consideration of the respective covenants, representations, warranties and agreements set forth herein, the Parties hereto agree as follows:

Article 1.
DEFINITIONS

For purposes of this Agreement, the following capitalized terms have the following meanings.

1.1. "Action" has the meaning set forth in Section 13.3.1 (Jurisdiction).

1.2. "Additional Third Party Agreement" has the meaning set forth in Section 2.3 (Additional Rights after Prior Agreement Execution Date).

1.3. "Affiliate" of an entity means any other entity that, directly or indirectly, through one or more intermediaries, controls, is controlled by, or is under common control with such first entity. For purposes of this definition only, "control" (and, with correlative meanings, the terms "controlled by" and "under common control with") means the possession of the actual power to direct the management or policies of an entity, whether through the ownership of voting securities or by contract relating to voting rights or corporate governance. For clarity, as of the Execution Date, [**], which is engaged in the discovery, development and commercialization of microRNA therapeutics, is not an Affiliate of Isis because Isis has entered into an agreement pursuant to which Isis does

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

not have control of Regulus.

1.4. "API" means the active pharmaceutical ingredient of the Product.

1.5. "apoB" means apolipoprotein B.

1.6. "Approval" means, with respect to any Product in any regulatory jurisdiction, approval from the applicable Regulatory Authority sufficient for the manufacture, distribution, use and sale of the Product in such jurisdiction in accordance with Applicable Laws. In jurisdictions where the applicable Regulatory Authority sets the pricing authorizations for a Product, Approval will not be deemed to have occurred until the earlier of (a) Genzyme or its Sublicensee and the Regulatory Authority have determined pricing, or (b) ninety (90) days after approval (whether national or centralized) is received for the applicable Regulatory Authority sufficient for the manufacture, distribution, use and sale of the Product in such jurisdiction (other than pricing authorization for the Product) in accordance with Applicable Laws.

1.7. "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, but excluding patent and copyright laws.

1.8. "ASO Product" any preparation in final form for sale by prescription, over-the-counter or any other method for any indication, including human or animal use, which contains one or more oligonucleotides or an analog thereof that [**].

1.9. "Bankruptcy Code" has the meaning set forth in Section 14.13 (Rights in Bankruptcy).

1.10. "Calendar Quarter" means the respective periods of three (3) consecutive calendar months ending on March 31, June 30, September 30 or December 31.

1.10. "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, or (b) except in the case of a bona fide equity financing in which a Party issues new shares of its capital stock, a transaction or series of related transactions in which a Third Party, together with its Affiliates, becomes the beneficial owner of fifty percent (50%) or more of the combined voting power of the outstanding securities of such Party, or (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, but excluding any financial factoring arrangements.

1.12. "Commercially Reasonable Efforts" means, (a) with respect to the research, development or commercialization by Genzyme of a Product, at any given time as the case may be,

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

efforts reasonably used by Genzyme or its Affiliates (giving due consideration to relevant industry standards) for Genzyme's own products (including internally developed, acquired and in-licensed products) with similar commercial potential at a similar stage in their lifecycle (assuming continuing development of such product), taking into consideration their safety, tolerability and efficacy, the profitability (taking into account any payments payable under this Agreement), the extent of market exclusivity, patent protection, cost to develop the product, promotable claims and health economic claims and (b) with respect to the research and development by Isis of a Product, at any given time as the case may be, efforts reasonably used by an entity in the biotechnology/pharmaceutical industry of similar resources and expertise as Isis, for such similar entity's own products (including internally developed, acquired and in-licensed products) with similar commercial potential at a similar stage in their lifecycle (assuming continuing development of such product), taking into consideration their safety, tolerability and efficacy, the profitability (taking into account any payments payable under this Agreement), the extent of market exclusivity, patent protection, cost to develop the product, promotable claims and health economic claims.

1.13. "Commercial Scale Manufacturing IP" means any confidential or patented scientific or technical data, information, method, technique, protocol, invention or processes that has been found to be useful for commercial scale manufacturing facility but is not generally useful for manufacturing oligonucleotides on a non-commercial scale, including all manufacturing plant designs, plans diagrams and descriptions and also including all regulatory filings.

(a) For illustrative purposes only and not as a limitation, the following would be considered to be Commercial Scale Manufacturing IP:

(i) Piping and Instrumentation Diagrams (P&ID) for a Genzyme manufacturing facility;

(ii) Design plans and schematics for a Genzyme manufacturing facility (including tank farms, synthesis and purification suites, and analytical testing laboratories);

(iii) Operating Documents, for example batch records, SOPs, validation master plans;

(iv) Floor plans and equipment layout drawings for a Genzyme manufacturing facility; and

(v) Regulatory filings.

(b) For illustrative purposes only and not as a limitation, the following would not be considered to be Commercial Scale Manufacturing IP:

(i) Discovery that a particular side reaction leads to an unexpected impurity;

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

(ii) Discovery regarding how to avoid the impurity or how to remove it.

(iii) Development of the use of alternative reagents;

(iv) Discovery of recycle possibilities;

(v) Discovery to enhance yields;

(vi) Discovery of the Mipomersen oxidant;

(vii) Development and validation of QbD/Design Space filing strategy.

(viii) Development and validation of PAT measures.

1.14. "Confidential Information" has the meaning set forth in Section 12.1 (Non-Disclosure).

1.15. "Control" or "Controlled" means, with respect to any Know-How, Patent or other intellectual property right or Regulatory Materials, possession by a Party (including its Affiliates) of the right (whether by ownership, license or otherwise) to grant to the other Party a license or a sublicense under such Know-How, Patent or other intellectual property right or access to Regulatory Materials without violating the terms of any agreement or other arrangement with any Third Party.

1.16. "Cover," "Covered" or "Covering" means, with respect to a Patent and the subject matter at issue, that, but for a license granted under an issued claim included in such Patent, the manufacture, use, sale, offer for sale or importation of the subject matter at issue would infringe such claim or, in the case of a Patent that is a patent application, would infringe a claim in such patent application if it were to issue as a patent.

1.17. "Development Budget" means the initial written development budget attached hereto as Exhibit B setting forth, for the time period covered by the Development Plan, the budget for the development of the Product during the applicable time period, as it may be updated and amended by the JDC or the Parties during the Term in accordance with this Agreement.

1.18. "Development Expenses" means internal or external expenses incurred in accordance with the Development Plan and the Development Budget, including the costs of all clinical trials and preclinical studies, including post-marketing trials. The types of expenses included in this category are investigator grants, laboratory services, clinical PK assays, carcinogenicity studies, CMC studies, CRO services and pass-throughs, pharmacovigilence 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 & DP), investigator meetings, monitoring, SAB costs, DSMB costs, key opinion leader costs, program specific travel, metabolomics assays, courier services and clinical trial liability insurance costs. Development Expenses include quality assurance costs for auditing clinical trial activities and preclinical studies support (report reviews and CMC

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

review). When a Party is a manufacturer of the Product under development, Development Expenses include such Party's Fully Absorbed Cost of Goods.

1.19. "Development Plan" means the initial written development and regulatory plan attached hereto as Exhibit A for the Product as it may be updated and amended during the Term by the JDC or the Parties in accordance with this Agreement.

1.20. "Development Program" means the program to be conducted by the Parties in accordance with an approved Development Plan to develop and obtain Approval of the Product in the Territory, all as more fully described in Article 5 (Development).

1.21. "Disclosure Schedule" means the schedule delivered by Isis to Genzyme that includes exceptions to Isis' representations and warranties in Section 10.2 (Isis Representations and Warranties) hereof.

1.22. "Dispute" has the meaning set forth in Section 13.1 (Dispute Resolution Mechanism).

1.23. "Effective Date" means January 30, 2008.

1.24. "Execution Date" has the meaning set forth in the preamble.

1.25. "EMEA" means the European Regulatory Authority known as the European Medicines Agency and any successor agency thereto.

1.26. "Encumbered Follow-On Compound" has the meaning set forth in Section 2.4 (Follow-On Compound).

1.27. "Executives" has the meaning set forth in Section 13.1 (Escalation to Senior Management).

1.28. "External Development Expenses" means Development Expenses other than Internal Development Expenses. For clarity, External Development Expenses include the manufacturing Party's Fully Absorbed Cost of Goods.

1.29. "External Sales & Marketing Expenses" means Sales & Marketing Expenses other than Internal Sales & Marketing Expenses.

1.30. "FDA" means the United States Food and Drug Administration and any successor agency thereto.

1.31. "FH" means familial hypercholesterolemia.

1.32. "Fixed Costs" means the cost of facilities, utilities, insurance (including any accrual for self-insurance), facility and equipment depreciation, and other fixed costs directly attributable to the applicable activity, allocated based upon the proportion of such costs directly attributable to the support or performance of the applicable activity in accordance with the Development Plan or the Product's manufacturing or commercialization plan, as

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

the case may be. Fixed Costs will be determined in accordance with GAAP.

1.33. "Follow-On Compound" means all pharmaceutical compositions, formulations, dosage forms, delivery systems and presentations that contain [**] apoB (alone or with other active ingredients) other than Mipomersen.

1.34. "Follow-On Compound Encumbrances" has the meaning set forth in Section 2.4.2.

1.35. "Fully Absorbed Cost of Goods" means:

(a) with respect to units of Product produced by Genzyme, the Variable Costs and Fixed Costs incurred by Genzyme to the extent associated with the manufacture (inclusive of finishing processes including filling, packaging, labeling and other preparation), quality assurance, quality control and other testing, storage and shipping of batches of such units of Product;

(b) with respect to units of Product manufactured by Isis, the costs incurred by Isis as determined using the methodology set forth in Schedule 1.35, which Schedule will be updated by Isis on an annual basis in advance of each fiscal year (with material changes to such methodology subject to Genzyme's prior agreement); and

(c) with respect to units or components of Product that are not manufactured by the Parties, the amounts paid to the vendor plus costs associated with acquisition from such vendor.

If a facility that is used to manufacture Product has the capacity to manufacture products for other programs of either Genzyme or Isis outside of the activities contemplated by this Agreement, the Fixed Costs component of the Fully Absorbed Cost of Goods will be allocated in proportion to the actual use of such facility for the manufacture of Product pursuant to this Agreement and the capacity to manufacture products for such other programs outside of this Agreement in a manner that is mutually agreeable to the Parties. No idle capacity of a manufacturing facility, or a proportionate use thereof, will be included in Fully Absorbed Cost of Goods unless such capacity or facility was built specifically to manufacture Product and is not being used to manufacture any other products, in which case the depreciation associated with such idle capacity will be included in Fully Absorbed Cost of Goods to the extent that such facility is in service. Fully Absorbed Cost of Goods will exclude all costs otherwise reimbursed pursuant to this Agreement. Fully Absorbed Costs of Goods will be determined in accordance with GAAP. Genzyme will use commercially reasonable efforts to minimize and mitigate circumstances that would result in idle capacity being included in Fully Absorbed Cost of Goods.

1.36. "G&A Costs" will mean the costs of general and administration services (including legal, finance, accounting, human resources and other general and administrative support services) as reasonably required to support the activities of the Parties under this

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

Agreement, which costs will be determined and reported in accordance with GAAP and in good faith by each Party.

1.37. "GAAP" means then-current United States generally accepted accounting principles, consistently applied.

1.38. "Genzyme" has the meaning set forth in the preamble.

1.39. "Genzyme Indemnitees" has the meaning set forth in Section 10.3.2 (Indemnification by Isis).

1.40. "Genzyme Manufacturing Improvements" has the meaning set forth in Section 9.3.2(b) (Terms of Sharing Program).

1.41. "Genzyme Program IP" means the Genzyme Program Patents, Genzyme Program Know-How and any work-of-authorship authored in the performance of the Development Program or Research Programs solely by Genzyme's employees or Third Parties acting on Genzyme's behalf.

1.42. "Genzyme Program Know-How" means any and all Know-How which is made or conceived during and in connection with the conduct of the Development Program or the Research Programs or commercializing the Product solely by Genzyme's employees or Third Parties acting on Genzyme's behalf.

1.43. "Genzyme Program Patents" means any and all Patents Controlled by Genzyme that Cover Genzyme Program Know-How.

1.44. "IND" means an Investigational New Drug Application, as defined in the US Federal Food, Drug, and Cosmetic Act, as amended from time to time (21 U.S.C. Section 301 et seq.), together with any rules and regulations promulgated thereunder, or similar application or submission that is required to be filed with any Regulatory Authority before beginning clinical testing of a Product in human subjects.

1.45. "Indemnitee" has the meaning set forth in Section 10.3.3 (Indemnification Procedure).

1.46. "Indemnifying Party" has the meaning set forth in Section 10.3.3 (Indemnification Procedure).

1.47. "Infringement Claim" has the meaning set forth in Section 9.6.1 (Notice).

1.48. "In-Licensed Third Party IP" means Patents or Know-How Controlled by Isis that are licensed to Isis pursuant to a Third Party Agreement.

1.49. "Internal Development Expenses" means Development Expenses attributable to the internal costs of base salary plus a factor for reasonable and customary employee benefits and payroll taxes for those employees and temporary employees directly responsible for performing the development activity, plus program specific travel for such employees

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

and temporary employees, plus G&A Costs, or other overhead costs; provided, however, that where the Product is being manufactured by a Party, Internal Development Expenses will not include such Party's Fully Absorbed Cost of Goods. A hypothetical example illustrating the methodology Genzyme currently uses to calculate its Internal Development Costs is set forth in Schedule 1.49.

1.50. "Internal Sales & Marketing Expenses" means Sales & Marketing Expenses attributable to the internal costs of base salary and commissions payable to employees plus a factor for reasonable and customary employee benefits and payroll taxes for those employees directly responsible for performing the sales and marketing activity, plus sales and marketing specific travel for such employees, plus G&A Costs or other overhead costs.

1.51. "Isis" has the meaning set forth in the preamble.

1.52. "Isis Core Technology Patents" means all Patents Controlled by Isis or any of its Affiliates as of the Prior Agreement Execution Date or during the Term, including Isis Program Patents and Joint Patents, that are necessary or useful for the development and commercialization of Product, including the Patents identified on Schedule 1.52, in each case other than Product-Specific Patents, Licensed Product Patents and Isis Manufacturing and Analytical Patents.

1.53. "Isis Database" has the meaning set forth in Section 6.4 (Isis Safety Database).

1.54. "Isis Indemnitees" has the meaning set forth in Section 10.3.1 (Indemnification by Genzyme).

1.55. "Isis Manufacturing and Analytical Know-How" means Know-How other than Product Know-How Controlled by Isis or its Affiliates as of the Prior Agreement Execution Date or during the Term, including Isis Program Know-How and Joint Know-How, that relates to the synthesis or analysis of Products independent of sequence or chemical modification.

1.56. "Isis Manufacturing and Analytical Patents" means Patents Controlled by Isis or its Affiliates as of the Prior Agreement Execution Date or during the Term, including Isis Program Patents and Joint Patents, that claim methods and materials used in the synthesis or analysis of Products independent of sequence or chemical modification, including the Patents identified on Schedule 1.56. Isis Manufacturing and Analytical Patents do not include the Product-Specific Patents, Licensed Product Patents and the Isis Core Technology Patents.

1.57. "Isis Manufacturing and Analytical IP" means the Isis Manufacturing and Analytical Know-How and Isis Manufacturing and Analytical Patents solely to the extent necessary or useful to manufacture a Product.

1.58. "Isis Manufacturing Improvements" has the meaning set forth in Section 9.3.2(c) (Terms of Sharing Program).

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

1.59. "Isis Program IP" means the Isis Program Patents and Isis Program Know-How and any works-of-authorship authored in the performance of the Development Program or Research Programs solely by Isis' employees or Third Parties acting on Isis' behalf.

1.60. "Isis Program Know-How" means any and all Know-How which is made or conceived in the performance of the Development Program or the Research Programs solely by Isis' employees or Third Parties acting on Isis' behalf.

1.61. "Isis Program Patents" means any and all Patents Controlled by Isis that Cover Isis Program Know-How.

1.62. "Joint Development Committee" or "JDC" has the meaning set forth in Section 4.1.1 (Establishment of JDC).

1.63. "Joint Know-How" means any and all Know-How that is made or conceived in the performance of the Development Program or the Research Programs jointly by Isis' and Genzyme's employees or others acting on Isis' and Genzyme's behalf.

1.64. "Joint Patent Committee" or "JPC" has the meaning set forth in Section 4.2.1 (Establishment of the JPC).

1.65. "Joint Patents" means any and all Patents that Cover Joint Know-How.

1.66. "Joint Program IP" means Joint Patents, Joint Know-How and any works-of-authorship authored in the performance of the Development Program or Research Programs jointly by Isis' and Genzyme's employees or others acting on their behalf.

1.67. "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.

1.68. "Licensed IP" means the Licensed Patents, the Product Know-How, the Isis Manufacturing and Analytical Know-How; provided, however, that (a) for any such Know-How or Patent that becomes Controlled by Isis after the Prior Agreement Execution Date pursuant to an Additional Third Party Agreement, the provisions of Section 2.3 (Additional Rights after Prior Agreement Execution Date) will govern whether such Know-How or Patent will be included as Licensed IP and (b) with respect to any Follow-On Compound, the provisions of Section 2.4 (Follow-On Compound) will govern the extent to which In-Licensed Third Party IP will be included in Licensed IP.

1.69. "Licensed Patent(s)" means the Licensed Product Patents, Isis Core Technology Patents and Isis Manufacturing and Analytical Patents.

1.70. "Licensed Product Patents" means (i) the [**] Patent, and (ii) any Patent Controlled by

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

Isis during the Term, including any Isis Program Patents and Joint Patents, claiming (a) [**] apoB, (b) the sequence of apoB, (c) the specific composition of matter of a Product, or (d) methods of using Product as a therapeutic, methods of using Product to modulate apoB, and methods of using the Product to inhibit expression of apoB; and also claiming or describing (x) [**], or (y) methods of using such nucleic acids as a therapeutic or to modulate a gene target [**]. Notwithstanding the foregoing, a Patent that has been issued for at least two years that claims (a), (b), (c) or (d) above and that also describes, but does not claim, (x) or (y) above, will be a Product-Specific Patent, not a Licensed Product Patent

1.71. [**].

1.72. "[**] Manufacturing Improvements" has the meaning set forth in Section [**].

1.73. "MAA" means a marketing authorization application filed with (a) the EMEA under the centralized EMEA filing procedure or (b) a Regulatory Authority in any Major European Country if the centralized EMEA filing procedure is not used, after completion of clinical trials to obtain marketing approval.

1.74. "MAA Approval" means the Approval of a MAA for the applicable Product in any of the Major European Countries.

1.75. "Major European Country" means France, Germany, Italy, Spain, or the United Kingdom.

1.76. "Major Market Countries" means Canada, the United States, Japan and each Major European Country.

1.77. "Manufacturing Improvements" means any and all scientific and technical data, information, methods, techniques, protocols, inventions, and processes that have been found to be useful in the manufacture of ASO Products, excluding Commercial Scale Manufacturing IP.

1.78. "Mipomersen" means mipomersen sodium, formerly known as ISIS 301012, including all pharmaceutically acceptable salts, solvates, hydrates, hemihydrates, metabolites, pro-drug forms, stereoisomers, enantiomers, racemates and all optically active forms thereof.

1.79. "NDA" means a New Drug Application filed with the FDA after completion of clinical trials to obtain marketing approval for the applicable Product in the United States.

1.80. "NDA Approval" means the Approval of an NDA by the FDA for the applicable Product in the U.S.

1.81. "NDA Filing" means the acceptance by the FDA of the filing of an NDA for the applicable Product.

1.82. "Net Profits or Losses" means Net Revenues less Program Costs. To the extent Net

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

Revenues exceed Program Costs for the relevant period, the amount of such difference will be deemed "Net Profits," and, to the extent Program Costs exceed Net Revenues for the relevant period, the amount of such difference will be deemed "Net Losses."

1.83. "Net Revenue" during the relevant period means the sum of (a) Net Sales, if any, of Products in the Territory during such period, plus (b) all revenue received by either Party or their respective Affiliates from a Third Party in consideration for the grant of a right to make, use, sell, offer for sale or import a Product in the Territory, including monies received pursuant to a license with a Third Party such as upfront fees, milestones and royalties,

and monies received for marketing rights or distribution rights. If Genzyme or its Affiliates receives non-cash consideration for the grant of a right to make, use, sell, offer for sale or import a Product in the Territory, the Parties will agree in good faith on the valuation of such consideration to be included in Net Revenue.

1.84. "Net Sales" means the gross invoiced sales amount of the Product billed by Genzyme or its Affiliates or Sublicensees, in each case to independent Third Parties, including to distributors and end-users, for the sale or other commercial disposition of the Product in the Territory, less the following items ("Net Sales Adjustments") as applicable to such Product to the extent actually taken or incurred with respect to such sale:

(a) credits or allowances for returns, rejections or recalls (due to spoilage, damage, expiration of useful life or otherwise), retroactive price reductions or billing corrections;

(b) invoiced freight, postage, shipping and insurance, handling and other transportation costs;

(c) sales, use, value added and other similar taxes (excluding income taxes), tariffs, customs duties, surcharges and other governmental charges levied on the production, sale, transportation, delivery or use of the Product in the Territory that are incurred at time of sale or are directly related to the sale (which in all cases will be the direct responsibility of the selling Party); and

(d) quantity, cash or other trade discounts, rebates, refunds, charge backs, fees, credits or allowances (including amounts incurred in connection with government-mandated rebate and discount programs, Third Party rebates and charge backs, and hospital buying group/group purchasing organization administration fees and payor organizations), distribution fees, sales commissions, and commissions paid to Third Parties;

all in accordance with standard allocation procedures, allowance methodologies and accounting methods consistently applied, in accordance with GAAP.

Notwithstanding the foregoing, the following will not be included in Net Sales: (1) Genzyme's transfer of Product to an Affiliate, (2) Product provided by Genzyme or an Affiliate for administration to patients enrolled in clinical trials or distributed through a not-for-profit foundation at no charge to eligible patients, provided, however, that

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

Genzyme or its Affiliate receive no consideration from such clinical trials or not-for-profit foundation for such use of Product and (3) Product used as samples to promote additional Net Sales, in amounts consistent with normal business practices of Genzyme.

1.85. "[**]" has the meaning set forth in Section [**].

1.86. "[**] Process" has the meaning set forth in Section [**].

1.87. "Participating Isis Partner" means any Third Party that has a then-current contractual relationship with Isis pursuant to which (i) such Third Party is required to disclose to Isis on at least an annual basis any Manufacturing Improvements invented or developed by such Third Party, and (ii) Isis has the right to license such Third Party's Manufacturing Improvements to Genzyme under this Agreement and in accordance Section 9.3.2 (Terms of Sharing Arrangement), and (iii) such Third Party is either (A) [**] or [**], (B) manufacturing at least 50% of its requirements for the active pharmaceutical ingredient for an ASO Product under license from Isis on its own behalf or through Isis (i.e., it is not using a Third Party manufacturer to manufacture such portion of such active ingredient) or (C) maintaining an ongoing and substantial internal process development program related to the manufacture of ASO Products.

1.88. "Party and Parties" has the meaning set forth in the preamble.

1.89. "Patent(s)" 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).

1.90. "Permitted Licenses" means licenses granted by Isis after the Effective Date to any Third Party under the Isis Core Technology Patents or the Isis Manufacturing and Analytical IP (but not under the Licensed Product Patents or for use of the [**]) 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 [**], where such Third Party is primarily engaged in providing contract manufacturing or services and is not engaged in drug discovery, development or commercialization. Notwithstanding the foregoing, Permitted Licenses do not include any licenses that allow (i) a Third Party to make, use or sell an oligonucleotide having the same [**] as a Product or Isis' preferred [**]; (ii) a Third Party to manufacture any nucleic acid that (A) is designed to [**] apoB or (B) acts predominantly by [**] apoB, in each case ((A) or (B)), that will be incorporated into a therapeutic product for use in human clinical trials or for commercial sale; or (iii) Isis to directly supply to any Third Party any nucleic acid that any nucleic acid that (i) is designed to [**] apoB or (ii) acts predominantly by [**] apoB.

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

1.91. "Pivotal Trial" means a clinical study (whether or not denominated as a "Phase III" clinical study under applicable regulations) in human patients that is of size and design agreed to by a Regulatory Authority to be appropriate to establish that the Product is safe and effective for its intended use, to define warnings, precautions and adverse reactions that are associated with the Product in the dosage range to be prescribed, and to support Regulatory Approval of such Product.

1.92. "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, clinical development and commercialization.

1.93. "Primary Safety Contact Person" has the meaning set forth in Section 6.5 (Safety Reporting).

1.94. "Prior Agreement" has the meaning set forth in the recitals.

1.95. "Prior Agreement Execution Date" means January 7, 2008.

1.96. "Product" means all pharmaceutical compositions, formulations, dosage forms, delivery systems and presentations that contain Mipomersen or any Follow-On Compound as an active ingredient.

1.97. "Product Know-How" means Know-How Controlled by Isis on the Prior Agreement Execution Date or during the Term, including Isis Program Know-How and Joint Know-How, relating to or otherwise necessary for the development and commercialization of Product. Product Know-How does not include the Isis Manufacturing and Analytical Know How.

1.98. "Product License" means the license granted to Genzyme in Section 2.1 (Product License).

1.99. "Product-Specific Patents" means Patents Controlled by Isis or any of its Affiliates as of the Prior Agreement Execution Date and during the Term, including any Isis Program Patents and Joint Patents, claiming (a) [**] apoB, (b) the [**] of apoB, (c) the specific composition of matter of a Product, or (d) methods of using Product as a therapeutic, methods of using Product to modulate apoB, or methods of using the Product to inhibit expression of apoB, including the Patents identified on Schedule 1.99, other than Licensed Product Patents.

1.100. "Product Trademarks" means the trademark(s), service mark(s), accompanying logos, trade dress and/or indicia of origin used in connection with the distribution, marketing, promotion and commercialization of the Product in the Territory. For purposes of clarity, the term Product Trademark(s) will not include the corporate names and logos of either Party and will include any internet domain names incorporating such Product Trademarks.

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

1.101. "Program Costs" during the relevant period means all actual costs and expenses (including accruals chargeable against profits under GAAP) incurred (a) by either Party in the conduct of the Development Program (including all Development Expenses) (or the Research Program to the extent permitted under Section 7.2) and (b) by Genzyme, its Affiliates or Sublicensees pursuant to the manufacturing, sale, promotion and marketing of the Product in the Territory.

Program Costs will be determined and accounted for in accordance with Section 8.7.1 (Accounting). Each component of Program Costs will be allocated according to the allocation method mutually agreed to by the Parties under Section 8.7.2 (Allocation Methods). Program Costs will include:

(a) direct, out-of-pocket external costs and expenses, including clinical grants, clinical laboratory fees, positive controls and the cost of pre-clinical and clinical studies conducted and services provided by contract research organizations;

(b) Fully Absorbed Cost of Goods associated with the manufacture of preclinical, clinical and commercial grade materials;

(c) depreciation and/or amortization relating to (i) capital investments, (ii) process improvements or, (iii) any other capital expenditure for the construction or renovation of any manufacturing facility for the production of the Product;

(d) costs and expenses related to the conduct of clinical studies, including costs and expenses associated with data management, statistical designs and studies, document preparation and other expenses associated with the clinical testing program for the Product;

(e) costs and expenses associated with pharmacovigilence and risk management activities associated with the Product;

(f) costs and expenses of samples (without any mark-up) of Product provided by Genzyme to Isis;

(g) costs and expenses of preparing, submitting, reviewing or developing data or information for the purpose of submission of applications to obtain Approvals for the Product or maintenance of such Approvals (including user fees, establishment fees, product fees, or similar international maintenance fees);

(h) all royalties, milestones and license fees payable to Third Parties, including (i) those owed by Isis to [**] and [**] under the existing Third Party Agreements set forth on Schedule 10.2.2, and (ii) Genzyme's allocable portion of amounts due under any Additional Third Party Agreement in accordance with to Section 2.3 (Additional Rights after Prior Agreement Execution Date); provided, however that royalties, milestones and license fees payable under any Additional Third Party Agreement entered into in violation of Section 2.3 (Additional Rights After Prior Agreement Execution) will not be included in Program Costs;

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

(i) Sales and Marketing Expenses;

(j) costs and expenses associated with shipping, storage and distribution of the Product in the Territory, including (i) invoice, freight, postage, shipping, insurance, handling and other transportation charges to fulfill orders and not otherwise accounted for as Net Sales Adjustments, (ii) customer services, including collection of data about sales to hospitals, prescribers and end users, order entry, billing and adjustments, inquiry, credit and collection, (iii) cost of labor utilized for the distribution of the Product, (iv) duties and other monies paid to Third Parties pursuant thereto and (v) amounts paid to Third Parties with respect to storage or distribution of the Product;

(k) G&A Costs to the extent they are attributable to a Product;

(l) bad debt expense as calculated in accordance with GAAP;

(m) costs and expenses associated with any write-offs relating to (i) inventory, (ii) manufacturing costs and expenses, if applicable, (iii) product failures or (iv) associated regulatory compliance costs and expenses (each such write-off will be deemed Program Costs in the period in which they are incurred);

(n) damages (including out-of-court settlements) and out-of-pocket legal expenses (collectively "Damages") reasonably incurred by a Party or its Affiliates with respect to a Third Party claim or action arising out of the research, development, manufacture, use, distribution, marketing or sale of the Product within the scope of this Agreement (including Third Party Infringement Claims); provided, however, that such Damages (i) do not arise out of a claim or action that is subject to any indemnification obligation of Genzyme under Section 10.3.1 (Indemnification by Genzyme) or Isis under Section 10.3.2 (Indemnification by Isis), and (ii) are not incurred by either Party for activities conducted after the Term or conducted outside the scope of this Agreement;

(o) costs and expenses incurred in challenging Patents owned by Third Parties in accordance with Section 9.6.2 (Defense of Infringement Claim; Declaratory Judgment Actions) or 9.6.3 (Other Challenges);

(p) costs and expenses incurred enforcing intellectual property rights against Third Parties to the extent provided in Section 9.5.4 (Procedures and Expenses);

(q) costs and expenses relating to the filing, prosecution, maintenance and enforcement of Joint Patents and as provided in Section 9.4.2 (Election Not to Continue Prosecution; Abandonment), in each case in the Territory; and

(r) costs and expenses of insurance (including any product liability insurance or accrual for self-insurance).

For clarity, the following costs will not be considered Program Costs:

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

(a) the license fee or milestone payments payable by Genzyme to Isis pursuant to Section 8.1 or Section 8.2, respectively;

(b) Isis' costs and expenses of prosecuting and maintaining the Isis Core Technology Patents and Isis Manufacturing and Analytical Patents (other than as provided in Section 9.6.3 (Other Challenges));

(c) Genzyme's costs and expenses of prosecuting and maintaining the Product-Specific Patents and the Licensed Product Patents (other than as provided in Section 9.6.3 (Other Challenges));

(d) the costs and expenses of the mutually agreed upon Research Programs as described in Article 7 (Research Related to the Product);

(e) costs and expenses associated with stock-based compensation expenses or other pro forma adjustments to either Party's financials determined in accordance with U.S. GAAP;

(f) any costs and expenses of corporate overhead expenses, other than G&A Costs;

(g) unless otherwise deemed necessary for activities under this Agreement and mutually agreed by the Parties:

(A) amortization and depreciation expenses (unless consistent with Section 1.32 (Fixed Costs) hereof), deductions, credits, expenses including taxes and extraordinary or nonrecurring losses customarily deducted by a Party in calculating and reporting consolidated net income, manufacturing facility capital costs, capital expenditures, including purchases of facilities, property or equipment; and

(B) property taxes and any other taxes not related to the research, development, manufacture, commercialization or distribution of a Product in the Territory.

In addition, in no event will any amounts deducted from gross sales (Net Sales Adjustments) for the purpose of calculating Net Sales also be counted toward the amount of Program Costs.

Each of the following will be accounted for as a credit against Program Costs:

(a) to the extent provided in Section 9.5.5 (Recoveries), amounts recovered from an infringer of the Licensed IP;

(b) amounts received as insurance payments for damages, losses, costs or expenses previously included in the calculation of Program Costs; and

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

(c) tax refunds received to the extent they relate to tax payments previously deducted from Net Sales as a Net Sales Adjustment or Program Costs.

1.102. "Program IP" means Genzyme Program IP, Isis Program IP and Joint Program IP, collectively.

1.103. "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 Product in any country.

1.104. "Regulatory Materials" means any regulatory submissions, notifications, registrations, approvals and/or other filings and correspondence made to or with a Regulatory Authority in any country or jurisdiction in the Territory, and any other records required by Applicable Law to be maintained that may be necessary or useful to develop, manufacture, market, sell or otherwise commercialize Product in the Territory.

1.105. "Reporting Period" has the meaning set forth in Section 8.6.1 (Reports).

1.106. "Research Programs" has the meaning set forth in Section 7.1 (Research Programs).

1.107. "Responsible Party" has the meaning set forth in either Section 9.4.1(b)(i) or 9.4.1(d) as the context requires.

1.108. "Reversion" has the meaning set forth in Section 11.3.5(a)(iii) (Isis Reversion Rights).

1.109. "Sales & Marketing Expenses" means sales and marketing costs and expenses (including labor costs) incurred in connection with the sale, promotion and marketing of the Product in the Territory including (i) costs and expenses related to performing market research, post-marketing studies, advertising, producing promotional literature, sponsoring seminars and symposia, sales training meetings and seminars, originating sales, providing reimbursement, and other similar sales, marketing, and patient support services and (ii) all costs and expenses incurred for the sales force and sales force management by Genzyme, including costs and expenses related to salaries, commissions, current period reasonable and customary employee benefits and payroll taxes, sales incentive payments, sales training expenses, and travel expenses, all in accordance with GAAP.

1.110. "Sharing Agreement" means an agreement between Isis and a Participating Isis Partner pursuant to which (i) the Participating Isis Partner is required to disclose to Isis on at least an annual basis any Manufacturing Improvements invented or developed by such Third Party, and (ii) Isis has the right to license such Participating Partner's Manufacturing Improvements to Genzyme under this Agreement and in accordance Section 9.3.2 (Terms of Sharing Arrangement).

1.111. "Sharing Period" has the meaning given to it in Section 9.3.2(a) (Terms of Sharing Arrangement).

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

1.112. "[**] Patent" means Patent No. PCT/US[**].

1.113. "Special Isis Core Technology Patents" means (a) the Isis Core Technology Patents identified on Schedule 1.113 and all divisionals, continuations, substitutions, continuations-in-part of and similar applications claiming priority to any of the foregoing and 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 the foregoing, and (b) any other Isis Core Technology Patent that is similar to the Patents identified on Schedule 1.113 that Isis or its Affiliates come to Control after the Execution Date during the Term that Genzyme reasonably requests in writing be designated as a Special Isis Core Technology Patent.

1.114. "Sublicensee" means a Third Party who receives a sublicense of the Product License in accordance with Section 2.2 (Limited Right to Sublicense).

1.115. "Supply Agreement" means the Supply Agreement entered into between Genzyme and Isis pursuant to Section 5.3 (Clinical and Launch Supplies).

1.116. "Territory" means worldwide.

1.117. "Term" has the meaning set forth in Section 11.1 (Term).

1.118. "Third Party" means a person or entity other than the Parties, their respective Affiliates and their employees.

1.119. "Third Party Agreement" means any agreement with a Third Party now existing or entered into during the Term pursuant to which Isis obtains rights applicable to the development or commercialization of a Product.

1.120. "Third Party Claim" has the meaning set forth in Section 10.3.3 (Indemnification Procedure).

1.121. "Third Party Services Agreement" has the meaning set forth in Section 6.2.2 (Third Party Services Agreements).

1.122. "Variable Costs" means the cost of labor (which includes salaries and wages plus a factor for reasonable and customary employee benefits and payroll taxes for the applicable employees), raw materials, scrap, obsolescence, supplies, services, fees and other resources directly consumed or used in the conduct of the applicable activity in accordance with the Development Plan, or Genzyme's manufacturing or commercialization plan, as the case may be. All such cost determinations will be made in accordance with GAAP.

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

Article 2.
LICENSES

2.1. Product License. Isis hereby grants to Genzyme an exclusive license, with the limited right to sublicense as set forth in Section 2.2 (Limited Right to Sublicense), under the Licensed IP to research, develop, make, have made, use, sell, offer for sale, have sold, import and export Products in the Territory for therapeutic purposes. Notwithstanding the foregoing, (a) the exclusive license to the Isis Core Technology Patents will be subject to the licenses granted by Isis to Third Parties identified on Schedule 2.1 and Isis' right to grant Permitted Licenses and (b) with respect to any Follow-On Compound, the provisions of Section 2.4 (Follow-On Compound) will govern the extent to which In-Licensed Third Party IP is included within Licensed IP.

2.2. Limited Right to Sublicense.

2.2.1. The Product License is sublicensable only in connection with a sublicense of a Product to any Affiliate of Genzyme or to any Third Party, in each case for the continued research, development or commercialization of such Product in accordance with the terms of the Product License.

2.2.2. Notwithstanding the foregoing, the licenses granted to Genzyme under the Isis Manufacturing and Analytical IP are sublicensable to a Third Party [**] only in accordance with Section 6.3.1 (Manufacture).

2.3. Additional Rights after Prior Agreement Execution Date. After the Prior Agreement Execution Date, Isis may wish to in-license or acquire rights to Know-How or Patents Controlled by Third Parties (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 Licensed IP licensed to Genzyme under Section 2.1. In such event (and to the extent permitted by Isis' confidentiality agreement with the applicable Third Party), Isis will notify Genzyme regarding the nature of the technology and status of negotiations related to the Additional Third Party Agreement through the JDC. Once Isis has executed such Additional Third Party Agreement, Isis will offer such Third Party Patents or Know-How to Genzyme (which offer will include a description of the payments paid or potentially payable by Isis thereunder). At such time, if Genzyme wishes to include such Third Party Patents or Know-How under the license granted under Section 2.1, Genzyme will notify Isis of its desire to do so and the Parties will fairly and in good faith allocate upfront payments or ongoing payment obligations between Products and compounds that are not Products, if any, and other Isis licensees, if appropriate. As part of this allocation process, Isis will share with Genzyme, in reasonable detail, the assumptions and methodology Isis used to create the proposed allocation. If Genzyme does not agree to reimburse Isis for the amount of any upfront or similar acquisition payments fairly allocated to Product, and to be responsible for the payment of its share of any upfront, milestone, and royalty payments, then the Know-How or Patents acquired or in licensed by Isis under the Additional Third Party Agreement will not be considered Licensed IP licensed to Genzyme under the Product License. When Genzyme pays its share of any upfront, milestone, and royalty payments assumed by Genzyme under this Section 2.3, such payments will be considered Program Costs for the applicable Product. Except for Patents acquired by Isis as part of an acquisition of a Third Party's business,

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

before Isis in-licenses or acquire rights to any Patent Controlled by Third Parties which, if acquired, would be a Product-Specific Patent, Isis will first notify Genzyme in writing and allow Genzyme to license or acquire such Patent on the terms offered Isis. If Genzyme informs Isis that Genzyme is not interested in licensing or acquiring such Patent or does not license or acquire such Patent within 180 days of Isis' notice to Genzyme, then Isis will be free to in-license or acquire such Patent.

2.4. Follow-On Compound. The Parties contemplate that after the Effective Date Genzyme, either on its own or in collaboration with Isis, may wish to research, develop, and commercialize Follow-On Compounds. The scope of the In-Licensed Third Party IP included in Licensed IP under the Product License with respect to such Follow-On Compounds will be determined in accordance with the procedures set forth in this Section 2.4. At the time Genzyme intends to designate a Follow-On Compound as a development candidate, Genzyme will notify Isis in writing of such intention and will

describe in reasonable detail the applicable Follow-On Compound. Subject to Section 2.3 (Additional Rights after Prior Agreement Execution Date), if a Follow-On Compound utilizes any In-Licensed Third Party IP (an "Encumbered Follow-On Compound"), such In-Licensed Third Party IP will be included in Licensed IP only to the extent set forth below:

2.4.1. If the applicable Third Party Agreement contains a contractual obligation that would preclude Isis from including such In-Licensed Third Party IP in Licensed IP with respect to such Encumbered Follow-On Compound, then the In-Licensed Third Party IP that is the subject of such Third Party Agreement will not be included in Licensed IP.

2.4.2. If the applicable Third Party Agreement contains any potential encumbrances known by Isis and related to the potential Follow-On Compound, including field or territory restrictions, covenants, or milestones, royalty, sublicense revenue, or other payments ("Follow-On Compound Encumbrances"), Isis will fully disclose to Genzyme such Follow-On Compound Encumbrances and, if Genzyme agrees in writing to assume the Follow-On Compound Encumbrances (with any payments being included in Program Costs for such Encumbered Follow-On Compound), then the In-Licensed Third Party IP that is the subject of such Third Party Agreement will be included in Licensed IP.

2.4.3. If the applicable Third Party Agreement does not contain the obligations or encumbrances described in Sections 2.4.1 and 2.4.2 above, the In-Licensed Third Party IP that is the subject of such Third Party Agreement will automatically be included in Licensed IP.

2.4.4. If the applicable Third Party Agreement is or was also applicable to Mipomersen, then the In-Licensed Third Party IP that is the subject of such Third Party Agreement will automatically be included in the Licensed IP to the extent that (a) the terms of such Third Party Agreement do not preclude Isis from including it and (b) Genzyme agrees in writing to assume any applicable Follow-On

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

Compound Encumbrances associated with such Third Party Agreement.

2.4.5. Each time the Parties complete the process set forth above, Isis will update the schedules relating to Licensed Patents and Third Party Agreements, and Schedule 2.1 as appropriate.

2.5. Retained Rights. Subject to the terms and conditions of this Agreement, Isis retains the non-exclusive, non-transferable, non-licensable right under the Licensed IP only to the extent necessary for Isis to perform its obligations under this Agreement and the Supply Agreement.

2.6. Isis' Right of First Negotiation. With respect to any Genzyme Program IP that would be relevant to antisense therapies as a whole, including but not limited to, manufacturing, formulation and delivery technologies or oligonucleotide chemical modifications or the design of antisense therapeutics generally, then Genzyme hereby grants to Isis a right of first negotiation with respect to any exclusive license that Genzyme may elect to grant under such Genzyme Program IP (each, an "Antisense License") on the following terms and conditions:

2.6.1. General. Genzyme will not grant an Antisense License to any Third Party (or enter into discussions with, or solicit interest from, any Third Party regarding an Antisense License) unless and until:

(a) Genzyme gives written notice (the "Antisense License Notice") to Isis of Genzyme's interest in granting an Antisense License, which notice will identify in reasonable detail the proposed scope and terms and conditions of the license Genzyme proposes to grant; and

(b) (i) Isis notifies Genzyme that it declines the opportunity to negotiate with Genzyme regarding such a license, (ii) Isis does not indicate to Genzyme a desire to proceed with negotiations within forty-five (45) days after receipt of the Antisense License Notice, or (iii) Genzyme is otherwise permitted to enter into an Antisense License with a Third Party pursuant to Section 2.6.3 (Look Back).

2.6.2. Negotiation Period. If Isis notifies Genzyme, within forty-five (45) days after receipt of the Antisense License Notice, that it desires the opportunity to negotiate with Genzyme regarding such an Antisense License, the Parties will negotiate exclusively with each other for ninety (90) days (or such longer period as mutually agreed by the Parties) (the "Exclusive Negotiation Period") and will use commercially reasonable efforts to reach agreement regarding a mutually satisfactory Antisense License on commercially reasonable terms. During the Exclusive Negotiation Period, Genzyme will not enter into negotiations regarding an Antisense License with any Third Party.

2.6.3. Look Back. In the event that the Exclusive Negotiation Period expires before Genzyme and Isis have entered into an Antisense License, Genzyme will have no further obligation to negotiate with Isis with respect to any Antisense License in

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

any country in the Territory, and Genzyme will be free to grant one or more Antisense Licenses to one or more Third Parties in any country or countries in the Territory at Genzyme's sole discretion; provided, however, that for a period equal to the longer of (i) the Term plus one

(1) year or (ii) three (3) years following the expiration of the Exclusive Negotiation Period, Genzyme will not offer any Third Party an Antisense License containing a license scope and financial terms that are more favorable to the Third Party than the license scope and financial terms that Genzyme last offered to Isis during the Negotiation Period unless Genzyme first offers an Antisense License with such more favorable scope and terms to Isis in writing and Isis fails to accept such offer within fourteen (14) days after receiving it.

2.6.4. Non-Exclusive License. If Genzyme grants any Third Party a non-exclusive license under any Genzyme Program IP that would be relevant to antisense therapies as a whole, including but not limited to, manufacturing, formulation and delivery technologies or oligonucleotide chemical modifications or the design of antisense therapeutics generally, then Genzyme will promptly notify Isis of such license and will offer Isis a non-exclusive license under such licensed Genzyme Program IP with substantially similar scope and financial terms.

2.7. Third Party Agreements.

2.7.1. Exercise of Rights. Isis will exercise its rights under the Third Party Agreements in a manner that is as consistent as possible with the terms of this Agreement and in consultation with and as reasonably requested by Genzyme. Isis covenants that it will not, without Genzyme's prior written consent, agree, consent or acquiesce to any amendment, supplement or other modification to any Third Party Agreement or take any action under such Third Party Agreement or with respect to the intellectual property licensed thereunder that would adversely affect the rights granted to Genzyme under this Agreement, including under the Product License. Isis will immediately notify Genzyme of (a) any event that adversely affects the rights granted to Isis under a Third Party Agreement that are, in turn, sublicensed to Genzyme pursuant to this Agreement or (b) receipt by Isis of any notice of breach or termination of any Third Party Agreement. Isis will take all reasonable actions necessary, or permit Genzyme to take such actions, to maintain and enforce its rights under the Third Party Agreements in a manner that is consistent with the terms of this Agreement.

2.7.2. Sublicense Survival. Isis covenants that it will use good faith and Commercially Reasonable Efforts to enter into any necessary amendments or side agreements to its Third Party Agreements to ensure that (a) sublicenses under each Third Party Agreement will survive termination of such Third Party Agreement or (b) Genzyme will receive a direct license from the counterparty to each Third Party Agreement upon termination of such Third Party Agreement.

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

2.8. No Implied License. Except as expressly provided in this Agreement, neither 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. Without limiting the generality for the foregoing, a license to use Know-How will not be interpreted as an implied license under any Patent Rights other than as expressly provided in this Agreement.

Article 3.
EXCLUSIVITY

3.1. Non-Compete. During the Term, Isis and its Affiliates will not, directly or indirectly, and will not collaborate with, license or otherwise authorize any Third Party to, research, develop or commercialize any nucleic acid that (i) [**] apoB or (ii) [**] apoB, except pursuant to (a) the agreements identified on Schedule 2.1, as they existed on the Prior Agreement Execution Date, (b) Permitted Licenses, or (c) this Agreement.

3.2. [**] Technology. Without first obtaining Genzyme's written consent, which will not be unreasonably withheld, Isis will not license to a Third Party any technology that (a) is specifically useful in researching, developing or commercializing therapeutics whose primary purpose at the time of the license or primary therapeutic benefit at the time of commercialization is [**], (b) is not broadly applicable to other [**] and (c) was invented by Isis while performing activities pursuant to the Development Plan or pursuant to the Research Programs under Article 7 (Research).

Article 4.
JOINT COMMITTEES

4.1. Joint Development Committee.

4.1.1. Establishment of JDC. The Parties will establish a Joint Development Committee (the "JDC"), which will consist of a total of eight (8) members, with four (4) members from each Party, to oversee the Development Program. Members of the JDC may be represented at any meeting by a designee appointed by such member for such meeting. Each Party will be free to change its members on prior written notice to the other Party. The JDC will remain in place for four (4) years following the Effective Date; provided, however that if the commercial launch of the Product for a non-FH indication has not occurred by the end of such 4-year period, the Parties will mutually agree upon an appropriate extension of the JDC.

4.1.2. Responsibilities of the JDC. In addition to any responsibilities expressly described elsewhere in this Agreement, the JDC will:

(a) On a Calendar Quarter basis, review and evaluate progress under the Development Plan and expenditures relative to the Development Budget;

(b) Develop updates or amendments to the Development Plan and the Development Budget;

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

(c) Perform any other activities related to the Development Plan as jointly requested by both Parties from time to time;

(d) Review and approve a scientific and medical publication plan and medical affairs plan for the Product;

(e) Appoint one or more working group(s) to oversee particular activities to be performed under the Development Plan or create the scientific and medical publication plan and medical affairs plan for the Product, which working group(s) will dissolve no later than the date of the dissolution of the JDC.

For the avoidance of doubt, the JDC will have no authority to amend this Agreement.

4.1.3. Meetings; Minutes. During the course of implementing the Development Plan, the JDC will meet at least once each Calendar Quarter, and more frequently as the Parties mutually agree is appropriate, on such dates, in such places and at such times as the Parties will agree. The JDC will be chaired by Genzyme as of the Effective Date. The role of the chairperson will be to convene and preside at meetings of the JDC, but the chairperson will not be entitled to prevent items from being discussed or to cast any tie-breaking vote. Reasonably detailed written minutes will be kept of all JDC meetings and will reflect without limitation material decisions made at such meetings. The chairperson of the JDC will have responsibility for keeping minutes. Draft meeting minutes will be sent to each member of the JDC for review and approval within ten (10) business days after a meeting. Minutes will be deemed approved unless a member of the JDC objects to the accuracy or completeness of such minutes within thirty (30) calendar days of receipt.

4.1.4. Decision-Making and Dispute Resolution. The JDC will act by unanimous consent. The representatives of each Party will have collectively one vote on behalf of such Party; provided, however, that no such vote taken at a meeting will be valid unless at least one representative of each Party is present and participating in the vote. In the case of any matter which cannot be resolved unanimously by the JDC, at the written request of either Party, the dispute will be referred to senior management of the Parties in accordance with Section 13.1 (Escalation to Senior Management).

4.2. Joint Patent Committee.

4.2.1. Establishment of JPC. The Parties will establish a Joint Patent Committee (the "JPC") to discuss the continued prosecution of the Licensed Patents and Product-Specific Patents, (including Joint Patents). The JPC will be comprised of at least one (1) senior patent attorney from each Party. Each Party will be free to change its members at its sole discretion. The JPC will exist for so long as the JDC exists. Thereafter, the Parties will meet from time to time as necessary, or as may

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

be mutually agreed by the Parties, to discuss patent related issues.

4.2.2. Responsibilities of the JPC. At least once per Calendar Quarter, the JPC will meet (in person or by phone) to discuss prosecution strategy for the Licensed Patents and Product-Specific Patents (including Joint Patents) with the goal of maintaining the broadest coverage for the Product in accordance with Section 9.3 (Filing, Prosecution and Maintenance of Patents). Subject to Section 9.5 (Enforcement of Patents and Know-How) and Section 9.6 (Claimed Infringement by Third Parties), the JPC will also discuss any (a) potential Third Party infringement of the Licensed Patents and Product-Specific Patents (including Joint Patents) that might affect the Product and (b) Third Party intellectual property right that the Parties may want to license or challenge.

4.2.3. Decision-Making and Dispute Resolution. Subject to Section 9.3 (Filing, Prosecution and Maintenance of Patents), in the event a dispute relates to the prosecution or maintenance of a Patent, Genzyme will have the ultimate sole decision-making authority with respect to the Product-Specific Patents and Licensed Product Patents and Isis will have the ultimate sole decision-making authority with respect to the Isis Core Technology Patents and the Isis Manufacturing and Analytical Patents. Any other dispute at the JPC will be referred to the JDC for resolution.

4.3. Expenses. Each Party will be responsible for all of its own travel and related costs and expenses for its members (or designees) of the JDC and JPC and such expenses will not be treated as Program Costs.

Article 5.
DEVELOPMENT

5.1. Development Plan and Development Budget. The initial Development Plan and Development Budget through the end of 2009 that have been agreed to by the Parties as of the Execution Date are attached to this Agreement as Exhibit A and Exhibit B, respectively. The Parties acknowledge and agree that the Development Plan and Development Budget as of the Execution Date will need to be updated and augmented by the JDC on a quarterly basis and also from time to time in the discretion of the JDC. The purpose of the Development Plan is to (a) set forth a strategy and plan for development, manufacturing and Approval for the Product, (b) detail the responsibilities and activities of Isis and Genzyme with respect to the development of the Product and (c) specify the expected timing of such activities, including the estimated dates of the initiation and completion of such activities. The Development Budget contains the estimated costs associated with the tasks outlined in the Development Plan. The JDC (or directly by the written mutual agreement of the authorized representatives of the Parties) may amend the Development Plan and Development Budget at any time, but, in any event, the JDC will review and update the Development Plan and Development Budget by agreeing to a Development Budget for each calendar year during the Term not later than November 15th of the prior calendar year and prior to the commencement of each successive

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

calendar quarter during such calendar year. Any update or amendment to the Development Plan or Development Budget must be in writing. After the JDC has disbanded, if requested by either Party, Genzyme and Isis will meet as necessary at least annually on a mutually agreed schedule to review and evaluate progress under the Development Plan and expenditures relative to the Development Budget and to develop updates or amendments to the Development Plan and Development Budget, with decisions made by the Parties consistent with the principles contemplated for JDC decision making in Section 4.1.4 (Decision Making and Dispute Resolution).

5.2. Roles and Responsibilities.

5.2.1. Clinical Trials. The Development Budget includes the preclinical work and clinical trials to be conducted in and initiated in calendar year 2008 and classifies each item of preclinical work and clinical trials as "Isis Funded" or "Non Isis Funded." The JDC will assign specific responsibilities with respect to the conduct of such work and trials and will develop a written plan for transitioning responsibility between the Parties; provided, however, that such transition plan will not delegate the JDC's decision making authority to a Party. Except as otherwise determined by the JDC, Genzyme will conduct all clinical trials and all preclinical work for Mipomersen initiated in calendar year 2009 and thereafter. If pursuant to Section 4.1.4 (Decision-Making and Dispute Resolution) the JDC amends the Development Plan so as to increase the size or scope of a clinical study designated as "Isis Funded" (such as by increasing the number of patients or increasing the dosing period of a clinical study) and as a result of such increase the actual expenses associated with such study exceed [**]% of the amount budgeted for such study in the Development Budget as of the Execution Date, then the incremental cost and expenses for such study in excess of [**]% of such Development Budget amount will be considered "Non Isis Funded" (i.e. *not* "Isis Funded") for purposes of Section 8.3 (Financial Provisions Related to Development Activities).

5.2.2. Performance of the Development Program. Each Party will use Commercially Reasonable Efforts to conduct all activities and responsibilities assigned to it under the Development Plan and in accordance with the Development Budget and to cooperate with and provide reasonable support to the other Party in such other Party's conduct of activities under the Development Plan. Each Party will undertake its respective development activities, including its obligation to conduct clinical trials, in accordance with all Applicable Laws.

5.2.3. Responsibility. Except for those certain clinical trial responsibilities allocated to Isis as set forth in the Development Plan or other written document approved by the JDC, Genzyme will be responsible for all other aspects of the development of the Product.

5.3. Clinical and Launch Supplies. Isis will be responsible for manufacturing and supplying API for the Phase II clinical trials, the Pivotal Trial(s) and the initial commercial launch

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

of the Product, pursuant to a Supply Agreement the form of which is set forth on Exhibit C and a Quality Agreement the form of which is set forth on Exhibit D. In accordance with Section 8(a) and (b) of the Supply Agreement, the transfer price for the Product under the Supply Agreement will be Isis' Fully Absorbed Cost of Goods, and all amounts paid by Genzyme to Isis under the Supply Agreement will be Program Costs under this Agreement. The quantity of API that Isis will be required to supply for commercial launch will be mutually agreed by the Parties and set forth in the Supply Agreement. If Isis cannot manufacture as set forth above, upon written request by Genzyme, Isis will transfer to Genzyme all documentation and information, and permit Genzyme to reference and use any regulatory filings, and otherwise fully cooperate with Genzyme to enable Genzyme to make or have made the API for use by Genzyme in accordance with the Agreement. Genzyme will be responsible for all finished drug product and placebo needed for clinical trials of Product and finished drug product for commercial sale.

5.4. Know-How Transfer.

5.4.1. Transfer to Genzyme. During the existence of the JDC (or after the dissolution of the JDC at Genzyme's request), Isis will transfer to Genzyme and its representatives all material Product Know-How and Isis Manufacturing and Analytical Know-How within the possession or Control of Isis or any of its Affiliates, including all Regulatory Materials related to the Product; provided, however, that Isis will be required to deliver Isis Manufacturing and Analytical Know-How only to Genzyme or a Third Party manufacturer approved by Isis in accordance with Section 6.3 (Commercial Manufacture). Without limiting the generality of the foregoing:

(a) Before or promptly following the Execution Date, Isis will transfer any preclinical pharmacology and safety data, clinical data that then exists and any other information related to the Product that Genzyme may reasonably request. Thereafter during the Term, Isis will provide copies of all data from Isis' clinical or preclinical activities undertaken pursuant to the Development Plan.

(b) Isis will promptly disclose in reasonable detail and in a reasonable manner specified by Genzyme the Product Know-How and Isis Manufacturing and Analytical Know-How learned, discovered, developed, acquired or otherwise coming within the Control of Isis during the Term.

(c) At Genzyme's request from time to time during the Term, Isis will deliver to Genzyme copies (for documents and information) and samples (for materials) of any documents, files, diagrams, plans, specifications, designs, recipes, schematics, reports, models, prototypes, chemical or biologic materials, assays, reagents, or other tangible documentation or material in Isis' possession recording or embodying the Product Know-How and Isis Manufacturing and Analytical Know-How in Isis' or its Affiliate's possession.

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

(d) At Genzyme's request from time to time during the Term, and on a commercially reasonable schedule and at a commercially reasonable venue to be agreed on by the Parties, technically qualified personnel from each Party (and, if applicable, any Third Party manufacturer approved by Isis in accordance with Section 6.3 (Commercial Manufacture)) will meet and/or participate in telephone conference calls as reasonably necessary to exchange knowledge necessary to fully transfer all such Know-How.

(e) Section 2.2 (Limited Right to Sublicensee) and Article 12 (Confidentiality and Public Disclosures) will apply to any transfer of such Know How by Genzyme to a Third Party.

5.4.2. Transfer from Genzyme to Isis. Upon Isis' reasonable request, Genzyme will provide to Isis copies of any and all data from Genzyme's clinical or preclinical studies with the Product.

5.5. Subcontracting. Each Party may contract with one or more Third Party contractors to perform any or all of its obligations under the Development Plan; provided, however, that (a) except as otherwise agreed to by the JDC, each Third Party contractor will be approved by the JDC for the proposed work, such approval not to be unreasonably withheld, delayed or conditioned; and (b) the contracting Party provides the other Party with a true and accurate copy of each agreement pursuant to which such Third Party contractor is engaged promptly after execution thereof.

Article 6.
COMMERCIALIZATION AND REGULATORY MATTERS

6.1. Commercialization Responsibilities. Genzyme will have the exclusive right to commercialize any Product itself or through one or more Affiliates or Third Parties selected by Genzyme in the Territory and will have sole discretion, authority and responsibility in all matters relating to the commercialization of any Product in the Territory; provided, however, that Genzyme must use Commercially Reasonable Efforts to commercialize at least one Product in each of the Major Market Countries upon obtaining Approval in such country.

6.2. Regulatory Matters and Filings.

6.2.1. Regulatory Responsibility. Genzyme will be responsible for all regulatory matters relating to the Product in the Territory. Isis will transfer to Genzyme (or to a Genzyme Affiliate designated by Genzyme) the IND(s), orphan drug designation(s) and other existing Regulatory Materials for Mipomersen within thirty (30) days of the Execution Date. Between the Execution Date and the transfer to Genzyme of the IND related to the Product, Isis will not file or send any Regulatory Material related to the Product with or to any Regulatory Authority without Genzyme's prior written consent, which consent will not unreasonably withheld or delayed. Genzyme will prepare and file, in its own name, all NDAs, MAAs and other Regulatory Materials for the Product in the

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

Territory. Genzyme will have sole authority with respect to (a) obtaining Approvals for the Product and subsequently maintaining such Approvals, (b) communicating with Regulatory Authorities about the Product and (c) preparing and submitting supplements, communications, annual reports, adverse event reports, manufacturing changes, supplier designations and other related regulatory filings and Regulatory Materials. Isis will provide Genzyme with reasonable access to and copies of any documents or other materials Controlled by Isis that are useful for such regulatory filings and correspondence and maintenance of Approvals for the Product in the Territory and will otherwise cooperate with Genzyme's efforts to obtain and maintain Approval for the Product.

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

6.2.2. Third Party Services Agreements.

(a) Isis will exercise its rights under any agreement with a Third Party now existing or entered into during the Term pursuant to which Isis obtains services applicable to the pre-clinical or clinical development of a Product, including without limitation any agreement with a contract research organization (each a "Third Party Services Agreement") in a manner that is as consistent as possible with the terms of this Agreement and in consultation with and as reasonably requested by Genzyme. Isis covenants that it will not, without Genzyme's prior written consent, (i) agree, consent or acquiesce to any amendment, supplement or other modification to any Third Party Services Agreement or (ii) take any action under any Third Party Services Agreement, in each case that may adversely affect Genzyme as the holder of the Regulatory Materials related to the Product. Isis will take all reasonable actions necessary, or

permit Genzyme to take such actions, to maintain and enforce its rights under the Third Party Services Agreements in a manner that is consistent with the terms of this Agreement.

(b) In connection with the transfer of the Regulatory Materials for Mipomerson and Genzyme's assumption of responsibility for regulatory matters related to the Product, at Genzyme's written request Isis will use commercially reasonable efforts to promptly assign and transfer to Genzyme any Third Party Services Agreements solely related to the pre-clinical or clinical development of the Products. If the terms of any Third Party Services Agreement requires the consent of the other party thereto to effect such assignment, then upon Genzyme's request for an assignment, Isis will use commercially reasonable efforts to obtain such consent. In the event of any assignment to Genzyme under this Section 6.2.2, Genzyme will assume full responsibility for satisfying all obligations of Isis under any assigned agreement to the extent arising after such assignment and assumption, and Isis will remain responsible for satisfying all obligations under any assigned agreement to the extent arising prior to such assignment and assumption. If a Third Party Services Agreement relates both to the pre-clinical or clinical development of the Product and to the development of some other Isis product not licensed to Genzyme under this Agreement, then at Genzyme's request, the Parties will use commercially reasonable efforts to enter into such amendment(s) or new agreement(s) with the Third Party service provider to effect the transfer to Genzyme of all rights and obligations related to the Product under such Third Party Services Agreement.

6.2.3. Regulatory Audit. If a Regulatory Authority desires to conduct an inspection or audit of a Party's facility, or a facility under contract with a Party, with regard to a Product, then such Party will promptly notify the other Party and permit and cooperate with such inspection or audit, and will cause the contract facility to permit and cooperate with such Regulatory Authority and such other Party during such inspection or audit. Genzyme will have the right to have a representative observe such inspection or audit of a facility operated by Isis or under contract with Isis. Following receipt of the inspection or audit observations of such Regulatory Authority (a copy of which the audited Party will immediately provide to the other Party), the audited Party will prepare the response to any such

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

observations, and will provide a copy of such response to the other Party.

6.2.4. Class Generic Label Claims. Notwithstanding the foregoing, to the extent Genzyme intends to make any claims in a Product label that are of general applicability to antisense oligonucleotides, Genzyme will provide such claims to Isis in advance and will consider any proposals and comments made by Isis.

6.3. Commercial Manufacture.

6.3.1. Manufacture. Subject to Isis' obligation to manufacture and supply API for the commercial launch of the Product pursuant to Section 5.3 (Clinical and Launch Supplies) and the Supply Agreement, Genzyme will be responsible for securing commercial quantities of API and finished drug product for the Product. If Genzyme chooses not to manufacture the API for Product itself, then prior to using any Third Party manufacturer to supply commercial quantities of the API for Product, Genzyme must obtain Isis' prior written consent to the identity of the Third Party manufacturer and the material terms and conditions on which such Third Party manufacturer will supply commercial quantities of the API for Product, which consent will not be unreasonably withheld, conditioned or delayed; provided, however, that Isis will not withhold its consent to a Third Party manufacturer if its basis for doing so is an objection to the country in which such manufacturing will take place and the country in question is a member country of the European Union or Switzerland. In any event, Isis will cooperate with and provide commercially reasonable assistance to Genzyme and any approved Third Party manufacturer, including by transferring relevant Know-How in accordance with Section 5.4 (Know-How Transfer).

6.3.2. Assignment of Agreements With Third Parties. At Genzyme's written request in connection with the transfer of responsibility for manufacture, Isis will use commercially reasonable efforts to promptly assign and transfer to Genzyme any existing supply or other agreements solely related to the manufacture of the Products. Concurrent with the Execution of this Agreement, Isis will assign and transfer to Genzyme its agreement with [**] related to the preparation and packaging of drug product. If the terms of any of the agreements referred to in the previous two sentences require the consent of the other party thereto to effect such assignment, then upon Genzyme's request for an assignment, until Isis is able to obtain such consent and effect such assignment, Isis will exercise its rights under such agreements for the benefit of Genzyme and as reasonably requested by Genzyme. In the event of any assignment to Genzyme under this Section 6.3.2, Genzyme will assume full responsibility for satisfying all obligations of Isis under any assigned agreement to the extent arising after such assignment and assumption, and Isis will remain responsible for satisfying all obligations under any assigned agreement to the extent arising prior to such assignment and assumption.

6.4. Isis Safety Database. Isis maintains a database that includes information regarding the

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

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' drug compounds, Genzyme will reasonably cooperate in providing information to Isis to populate the Isis Database by providing Isis with copies of toxicology, pharmacokinetic

and serious adverse event final reports related to the Product, as well as any supporting data reasonably requested by Isis. Genzyme's obligation under this Section 6.4 will be subject to Applicable Law, any necessary informed consents and obligations to Third Parties.

6.5. Safety Reporting. Each Party will designate a primary contact person for the receipt of all reports called for in this Section 6.5 (the "Primary Safety Contact Person") and promptly notify the other Party of such designation or any change thereto. Each Party will notify the other Party's Primary Safety Contact Person of (a) all available information concerning any serious adverse event (SAE) occurring in patients treated with the Product, for any indication, (b) any information, regardless of source, which is relevant to known or potential human safety risks associated with the Product, (c) signals of human risk including information from *in vitro* or animal studies which may suggest a significant hazard to humans, including any findings from tests in laboratory animals that suggest a significant risk to human beings, including reports of mutagenicity, teratogenicity or carcinogenicity, and (d) information related to other products that are chemically similar to the Product or that have a pharmacologically similar mechanism of action (e.g., antisense oligonucleotides) that suggests a significant hazard for humans related to the Product. For purposes of this Section 6.5, a "serious adverse event (SAE)" is one which has an outcome which (i) is fatal or life threatening, (ii) requires or prolongs in-patient hospitalization, (iii) is a persistent or significant disability/incapacity, (iv) is a congenital anomaly/birth defect, or (v) is an important medical event, e.g., required medical or surgical intervention to prevent one of the other serious outcomes listed above. Each Party will promptly (but no later than twenty-four (24) hours after it becomes aware of the serious adverse event (SAE) or such other information and as necessary for compliance with regulatory requirements) provide the other Party with all such safety information through the receiving Party's Primary Safety Contact Person. Isis will conduct all safety reporting for the Product in accordance with Genzyme standard operating procedures communicated to Isis in writing. Upon transfer of the IND(s) to Genzyme and assumption by Genzyme of regulatory responsibilities under the IND(s), Genzyme will assume responsibility for the global safety database related to the Product. Genzyme will be solely responsible for reporting to Regulatory Authorities in accordance with the Applicable Law for expeditable adverse events and for periodic safety reporting relating to the safety of the Product and will furnish copies of such reports to Isis.

6.6. Commercial Forecasts & Plans.

6.6.1. In addition to the reports required under Section 8.6 (Periodic Reporting and Reconciliation), beginning on the last year in which the JDC is in place and each calendar year thereafter (1) not later than October 1st of the applicable year, Isis

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

will provide Genzyme with a non-binding, good-faith forecast of Isis' aggregate Program Costs for the following calendar year if any; and (2) not later than November 15th of the applicable year (i) Genzyme will provide Isis with a non-binding, good-faith forecast of Genzyme's aggregate Program Costs for the following calendar year, (ii) Isis will provide Genzyme with an updated non-binding, good-faith forecast of Isis' aggregate Program Costs for the following calendar year, if any, and (iii) based upon the Parties' non-binding forecasts of aggregate Program Costs, Genzyme will provide Isis with a non-binding, good-faith forecast of the Net Sales, Net Revenue and Net Profit for such year. Each Party's forecasts will include sufficient supporting detail to allow the other Party an opportunity to review and understand the forecasts.

6.6.2. Prior to the initial commercial launch of the Product and on an annual basis thereafter, Genzyme will provide Isis with a reasonably detailed written summary of its marketing plan and budget and will consider in good faith all comments and suggestions provided by Isis on such plans and budgets.

Article 7.
RESEARCH RELATED TO THE PRODUCT

7.1. Research Programs. The Parties will agree to conduct research programs related to the Product that may include, but are not limited to, the following research topics: (a) [**], (b) [**], (c) [**] and (d) [**] (collectively, the "Research Programs"). The nature and scope of the Research Programs will be determined within sixty (60) days of the Execution Date by a subcommittee to be appointed the JDC.

7.2. Research Funding. Isis will fund all external research expenses incurred in calendar years [**] in connection with the Research Programs. Genzyme will fund all external research expenses incurred in connection with the Research Programs in calendar year [**]. Thereafter, the Parties will agree upon allocation of any external research expenses incurred in connection with the Research Programs. Each Party will be responsible for their own internal research expenses incurred in connection with the Research Programs, and, unless otherwise agreed in writing by the Parties, internal and external research expenses incurred in connection with the Research Program will not be included as Program Costs. For the purposes of this Section 7.2, "internal research expenses" means costs and expenses incurred in connection with the Research Programs attributable to the internal costs of base salary plus a factor for reasonable and customary employee benefits and payroll taxes for those employees directly responsible for performing the research activity plus G&A Costs and other overhead expenses reasonably required to support the activities of the Parties under the Research Programs as allocated consistent with the methodologies agreed to under Section 8.7.2. Meanwhile, "external research expenses" means expenses incurred in connection with the Research Programs other than internal research expenses.

7.3. Research Efforts. If at any time during the Term no Product has received Approval in any Major Market Country and no Product is being developed pursuant to a Development

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

Plan, Genzyme will use Commercially Reasonable Efforts to conduct research activities designed to advance a Product to the stage where it can be developed pursuant to a Development Plan.

Article 8.
FINANCIAL PROVISIONS

8.1. Upfront License Fee. Genzyme will pay to Isis a non-refundable, non-creditable license fee of one hundred and seventy-five million dollars ($175,000,000) within five (5) days after the Execution Date.

8.2. Milestones.

8.2.1. Development Milestones.

(a) Mipomersen in FH. Within thirty (30) days after the achievement of the following indicated events by Genzyme, its Affiliate or its Sublicensee, Genzyme will pay Isis the following development milestone payments:

Milestone Event		Milestone Payment
NDA Filing for the use of Mipomersen to treat homozygous FH and/or patients who would be eligible under then-approved FDA labeling to receive low-density lipoprotein apheresis	$	[**]
NDA Approval for the use of Mipomersen to treat patients who have homozygous FH and/or who would be eligible under then-approved FDA labeling to receive low-density lipoprotein apheresis	$	[**]
MAA Approval for the use of Mipomersen to treat patients who have heterozygous FH or an otherwise comparably sized eligible patient population	$	[**]

(b) Mipomersen in Other Indications. Within thirty (30) days after the achievement of the following indicated events by Genzyme, its Affiliate or its Sublicensee, Genzyme will pay Isis the following development milestone payments:

Milestone Event*		Milestone Payment
NDA Approval for the use of Mipomersen to treat patients who have polygenic hypercholesterolemia or any patient population of a size comparable to the patient population deemed to be at "high risk" as determined in accordance with the National Cholesterol Education Program's clinical practice guidelines on	$	[**]

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

cholesterol management with LDL-C greater than or equal to [**] mg/dL		
MAA Approval for the use of Mipomersen to treat patients who have polygenic hypercholesterolemia or any patient population of a size comparable to the patient population deemed to be at "high risk" as determined in accordance with the National Cholesterol Education Program's clinical practice guidelines on cholesterol management with LDL-C greater than or equal to [**] mg/dL	$	[**]
Approval of a Japanese New Drug Application for the use of Mipomersen to treat patients who have polygenic hypercholesterolemia or any patient population of a size comparable to the patient population deemed to be at "high risk" as determined in accordance with the National Cholesterol Education Program's clinical practice guidelines on cholesterol management with LDL-C greater than or equal to [**] mg/dL	$	[**]

The Parties acknowledge that the current Development Plan contemplates *[one or more]* Pivotal Trials, that, if successful, are currently intended to achieve the milestones set forth in Section 8.2.1(b). To minimize the likelihood of any disagreement between the Parties around whether an Approval based upon a successful Pivotal Trial is sufficient to satisfy any of the milestones set forth in Section 8.2.1(b), the Parties agree to adopt the following process:

(1) Prior to final approval of any Pivotal Trial protocol or any material change to the protocol of an ongoing Pivotal Trial by the JDC, Genzyme will notify the JDC in writing if Genzyme believes, were a Regulatory Authority to grant an Approval for the treatment of a patient population that is co-extensive with the patient population(s) included for enrollment in such Pivotal Trial, that such approval will not qualify to meet the milestones set forth in Section 8.2.1(b).

(2) If Genzyme fails to provide the JDC with the notice contemplated by subsection (1) above, an Approval in the relevant jurisdiction for the treatment of a patient population that is co-extensive with the patient population(s) included for enrollment in the Pivotal Trial will be deemed to satisfy the applicable milestone in Section 8.2.1(b).

(3) In addition, in the event a Regulatory Authority proposes a limitation that would, in Genzyme's view, preclude the achievement of one of the milestones in Section 8.2.1(b), Genzyme will notify the JDC and in good faith attempt to avoid such restriction, to the extent practical under the circumstances. In such event, Genzyme will also reasonably consult with Isis regarding the best strategy to attempt to avoid such restrictions.

(c) Follow-On Compound. Within thirty (30) days after the achievement of the following indicated events by Genzyme, its Affiliate or its Sublicensee, Genzyme will pay Isis the following development milestone payments:

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

Milestone Event		Milestone Payment
NDA Approval for the Follow-On Compound	$	[**]
MAA Approval for the Follow-On Compound	$	[**]
Approval of a Japanese New Drug Application for the Follow-On Compound	$	[**]

8.2.2. Commercial Milestones. Within thirty (30) days after the achievement of the following indicated events by Genzyme, its Affiliate or its Sublicensee, Genzyme will pay Isis the following commercial milestone payments:

Milestone Event		Milestone Payment
Annual Net Revenues for all Products equals or exceeds three billion dollars ($3,000,000,000) in each of any two consecutive calendar years	$	250,000,000
Annual Net Revenues for all Products equals or exceeds four billion dollars ($4,000,000,000) in each of any two consecutive calendar years	$	250,000,000
Annual Net Revenues for all Products equals or exceeds five billion dollars ($5,000,000,000) in each of any two consecutive calendar years	$	250,000,000

In the event that more than one of the above commercial milestones is achieved simultaneously, Genzyme will make only one milestone payment, which will be for the milestone requiring the highest Annual Net Revenues. The Annual Net Revenues in any calendar year may be counted toward only one consecutive two calendar year period, except that if Annual Net Revenues for all Products equals or exceeds five billion dollars ($5,000,000,000) in any calendar year, that year may be counted as both the last year of one two consecutive year period and the first year of a second two consecutive year period. For the purpose of illustration, it will require at least five (5) years before Genzyme has been required to pay Isis the total of the seven hundred and fifty million dollars ($750,000,000) in milestone payments pursuant to this Section 8.2.2 (Commercial Milestone) unless Annual Net Revenue exceeds five billion dollars ($5,000,000,000) for three (3) or more consecutive years, in which case it would require four (4) years (assuming there was at least three billion dollars ($3,000,000,000) in sales in the first or fourth year during the four year period).

8.2.3. Hybrid Milestones. Within thirty (30) days after the achievement of the following indicated events by Genzyme, its Affiliate or its Sublicensee, Genzyme will pay Isis the following milestone payments:

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

Milestone Event*		Milestone Payment
The earlier to occur of (A) NDA Approval for the use of Mipomersen to treat patients who have heterozygous FH or an otherwise comparably sized eligible patient population; or (B) annual Net Revenues for all Products equals or exceeds two hundred and fifty million dollars ($250,000,000) in any calendar year	$	[**]
The earlier to occur of (A) NDA Approval for the use of Mipomersen to treat patients who have heterozygous FH or an otherwise comparably sized eligible patient population; or (B) annual Net Revenues for all Products equals or exceeds five hundred million dollars ($500,000,000) in any calendar year	$	[**]

* For purposes of clarification, if the first hybrid milestone above had not already been payable, and annual Net Revenues for all Products equals or exceeds five hundred million dollars ($500,000,000) in a calendar year, then both hybrid milestones would be triggered.

8.2.4. Milestones Payable Only Once. Once Genzyme has made any particular milestone payment under this Section 8.2, Genzyme will not be obligated to make any payment under this Section 8.2 with respect to the re-occurrence of same milestone, whether or not such re-occurrence is with respect to a different or the same Product or indication.

8.2.5. Indications of Mipomersen Approval. If Mipomersen receives an Approval for a label indication that is sufficiently broad to include the entire patient population contemplated by one or more development milestone(s) set forth in Sections 8.2.1(a) (Mipomersen in FH) or 8.2.1(b) (Mipomersen in Other Indications) or 8.2.3 (Hybrid Milestones), then Genzyme will pay Isis the milestone payment(s) for such development milestone(s), even though the indication for which Mipomersen is approved is not identical to the indication(s) of such development milestone(s).

8.3. Financial Provisions Relating to Development Activities.

8.3.1. Isis Funding of External Development Expenses.

(a) Subject to Section 5.2.1 (Clinical Trials), Isis will fund the clinical studies described as “Isis Funded” in the Development Budget.

(b) In addition to its funding obligations under Section 8.3.1(a) above, Isis will fund the first one hundred and twenty-five million dollars ($125,000,000) of the External Development Expenses for the Product that will be incurred by the Parties in accordance with the Development Plan starting as of January 1, 2008, including expenses for (a) the clinical studies described as “Non Isis Funded” in the Development Budget, (b) future clinical studies undertaken in accordance with the Development Plan, (c) toxicology studies undertaken in

accordance with the Development Plan (except for those described as "Isis Funded" in the Development Budget), (d) pharmacokinetic studies undertaken in accordance with

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

the Development Plan, (e) the manufacturing of API, as well as the packaging and distribution of the final Product and (f) the scientific advisory board and drug safety monitoring board. Any External Development Expenses that are recouped by Isis pursuant to Section 8.4 (Sharing of Net Revenue) will not be counted toward the fulfillment of this $125 million funding commitment. For purposes of clarity, in the event that Net Profit is achieved prior to the exhaustion of the Isis $125 million funding commitment set forth in this section 8.3.1, then for so long as Net Profit is maintained, Isis will not be obligated to fund External Development Expenses and the provisions of Section 8.5 (Sharing of Net Profits) will apply.

8.3.2. Shared Funding of External Development Expenses. After one hundred and twenty-five million dollars ($125,000,000) of External Development Expenses for the Product have been funded as described in Section 8.3.1(b) above, and after the sharing of Net Revenue in accordance with Section 8.4 (Sharing of Net Revenue), the Parties will share equally (on a 50/50 basis) all remaining External Development Expenses in any calendar year in which Net Profit is not achieved. In any calendar year in which Net Profit is achieved, the External Development Expenses will be included as Program Costs.

8.3.3. Internal Development Expenses. Each Party will be responsible for their own Internal Development Expenses with respect to development of the Product in any calendar year in which Net Profit is not achieved. In any calendar year in which Net Profit is achieved, the Parties' Internal Development Expenses will be included as Program Costs.

8.4. Sharing of Net Revenue. In any calendar year in which there is not a Net Profit, the Parties will share Net Revenue as follows:

8.4.1. Costs of Goods. Net Revenue first will be allocated between the Parties to reimburse them for the Fully Absorbed Cost of Goods incurred by the Parties in such calendar year.

8.4.2. External Sales & Marketing Expenses. Once the Parties have each been fully reimbursed for the Fully Absorbed Cost of Goods, Net Revenue next will be allocated between the Parties to reimburse them for External Sales & Marketing Expenses incurred by the Parties in such calendar year.

8.4.3. Internal Sales & Marketing Expenses. Once the Parties have each been fully reimbursed for the Fully Absorbed Cost of Goods and External Sales & Marketing Expenses, Net Revenue next will be allocated between the Parties to compensate them for Internal Sales & Marketing Expenses incurred by the Parties in such calendar year.

8.4.4. External Development Expenses. Once the Parties have each been fully reimbursed for the Fully Absorbed Cost of Goods, External Sales & Marketing Expenses and Internal Sales & Marketing Expenses, Net Revenue next will be

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

allocated between the Parties to compensate them for External Development Expenses incurred by the Parties in such calendar year (other than Fully Absorbed Cost of Goods already reimbursed under Section 8.4.1 above).

8.4.5. Internal Development Expenses. Once the Parties have each been fully reimbursed for the Fully Absorbed Cost of Goods, External Sales & Marketing Expenses, Internal Sales & Marketing Expenses and External Development Expenses, Net Revenue next will be allocated between the parties to compensate them for Internal Development Expenses incurred by the Parties in such calendar year.

8.4.6. Revenue Sharing Proportional to Expenses. For each category of cost or expense set forth in this Section 8.3, if Net Revenue is sufficient to only partially compensate the Parties for particular category of cost or expense, then the Parties will allocate the Net Revenue that may be allocated for such category between the Parties on a pro rata basis in proportion to the relative amounts of such category of cost or expense incurred by each Party.

8.5. Sharing of Net Profits.

8.5.1. Responsibility for Net Loss. Except as set forth in Section 8.4 (Sharing of Net Revenue), in any calendar year in which there is a Net Loss, Genzyme's share of Net Revenue will be one hundred percent (100%) and, subject to Section 8.3 (Financial Provisions Related to Development Activities), Genzyme will be solely responsible for all Program Costs. Isis will not be required to compensate Genzyme for any Net Loss.

8.5.2. Sharing of Net Profits. In any calendar year in which there is a Net Profit, the Parties will share such Net Profit in accordance with the following allocation based on Net Revenue for such calendar year:

Annual Net Revenue	Genzyme Percentage	Isis Percentage
$1 to ≤ $200 M	70%	30%

[**]	[**]	[**]
[**]	[**]	[**]
[**]	[**]	[**]
[**]	[**]	[**]
[**]	[**]	[**]
[**]	[**]	[**]
[**]	[**]	[**]
[**]	[**]	[**]
[**]	[**]	[**]
>$2 B	50%	50%

Notwithstanding the foregoing, in any calendar year in which Net Profits are generated in an amount greater than or equal to [**] of Net Revenue, Isis' share of

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

Net Profits will not fall below an amount equal to [**] of Net Revenue.

8.6. Periodic Reporting and Reconciliation.

8.6.1. Reports. Within thirty (30) days after the end of each Calendar Quarter during the Term (a "Reporting Period"), each Party will submit a written report to the other Party setting forth in reasonable detail the following, as applicable: (a) External Development Expenses incurred by Isis in accordance with Section 8.3.1 (Isis Funding of External Development Expenses) for each month during such Reporting Period, if any; (b) Fully Absorbed Costs of Goods, External Sales & Marketing Expenses, Internal Sales & Marketing Expenses, External Development Expenses, and Internal Development Expenses incurred by each Party for each month during such Reporting Period (if any); (c) actual Net Revenues, Net Sales and Program Costs incurred by or on behalf of the reporting Party for each month during such Reporting Period, if any, and (d) forecasts for the next four (4) Reporting Periods of Program Costs attributable to such Party (including, for each Party, the Fully-Absorbed Cost of Goods, External Sales & Marketing Expenses, Internal Sales & Marketing Expenses, External Development Expenses, and Internal Development Expenses) and, for Genzyme, Genzyme's estimate of Net Revenues. Such written reports will provide supporting detail for actual Net Revenues, Net Sales and Program Costs. The Parties recognize that the forecasts provided pursuant to subsection (d) are estimates only, and the Party providing such forecasts for the next Reporting Period will have no liability to the other Party based thereon. The Parties agree to consider in good faith the utilization of more rapid and detailed reporting mechanisms in order to meet the reporting requirements of the Parties. Development Expenses reported pursuant to this Section 8.5.1 will be included in Program Costs for determining Net Profits or Net Losses (and any revenue sharing or resulting funding obligations under Sections 8.3 and 8.4), as applicable, only to the extent made or incurred in accordance with the Development Plan and to the extent that they do not exceed the amount budgeted for such expense in the then-current Development Budget (if any) by more than [**] for a calendar year or as otherwise approved by the JDC. Costs and expenses included in Program Costs, as well as the deductions taken from Net Sales, will not be double counted (*i.e.*, any item of expense included in any expense category will not also be included in any other expense category).

8.6.2. Reconciliation.

(a) Within forty-five (45) days following the exchange of the reports under Section 8.6.1 (Reports), Genzyme will send to Isis a written report setting forth the calculation of any net amount owed by Genzyme to Isis (or by Isis to Genzyme), in order to ensure that (i) Isis fulfills its funding obligations under Section 8.3 (Financial Provisions Relating to Development Activities) and (ii) the Parties share Net Revenue as specified in Section 8.4 (Sharing of Net Revenue) or Net Profits as specified in Section 8.5.2 (Sharing of Net Profits). The Parties will

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

use the most recent forecasts for Annual Net Revenue and Net Profit provided pursuant to Section 8.6.1 (Reports) to determine the applicable Net Profit share in any given Calendar Quarter (other than in the final Calendar Quarter of any calendar year). The Parties will use the actual Annual Net Revenue and Net Profit for the calendar year to determine the applicable Profit Share percentage for the last Calendar Quarter in any calendar year.

(b) This reconciliation report will, among other things, contain (i) a tally of Isis' fulfillment of its funding obligations under Section 8.3 (Financial Provisions Relating to Development Activities), which tally will include any necessary adjustments, (ii) appropriate retroactive adjustments for prior Calendar Quarters in the same calendar year to take into account increases (or decreases) in Isis' share of Net Profits or Isis' fulfillment of its funding obligations under Section 8.3 (Financial Provisions Relating to Development Activities) and (iii) appropriate credit for Program Costs directly incurred by Isis.

8.6.3. Payments. If the reconciliation conducted under Section 8.6.2 (Reconciliation) results in a payment being owed by Genzyme to Isis, then the net amounts payable will be paid by Genzyme to Isis within forty-five (45) days of Genzyme receiving confirmation from Isis that

Genzyme's report required by Section 8.6.2 (Reconciliation) is accurate. If the reconciliation conducted under Section 8.6.2 (Reconciliation) results in a payment being owed by Isis to Genzyme, then the net amounts payable will be paid by Isis within forty-five (45) days of its receipt of the reconciliation report.

8.6.4. Disputes. In the event of a dispute regarding any amount reported by a Party pursuant to Section 8.6.1 (Reports) or the amount owed under Section 8.6.2 (Reconciliation), the Parties will promptly meet and negotiate in good faith a resolution to such dispute. In the event that the Parties are unable to resolve such dispute within sixty (60) days after notice by the disputing Party, the Parties will (a) use commercially reasonable efforts to reach agreement on the appointment of one internationally-recognized independent accounting firm to determine the matter or (b) if the Parties cannot reach agreement on such accounting firm, then each Party will appoint one internationally-recognized accounting firm and such firms will choose a third internationally-recognized independent accounting firm to make the final determination. Interest will be payable on any disputed amounts determined to be due in the same manner as provided for in Section 8.10 (Interest on Late Payments), with interest accruing from the end of the thirty (30) day period during which such payment should have been made.

8.7. Accounting and Allocation Methods.

8.7.1. Accounting. To the extent possible in accordance with the terms and conditions of this Agreement, the Parties will account for all amounts required to be determined under this Agreement (including Net Profits, Net Revenues, Program Costs, and all elements of any of the foregoing) in accordance with GAAP,

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

consistently applied. Where more than one accounting treatment is possible consistent with the terms and conditions of this Agreement and GAAP, each Party will account for amounts in a manner that is consistent with the manner in which such Party accounts for similar amounts for the purposes of its publicly reported financial statements.

8.7.2. Allocation Methods. Promptly upon the execution of this Agreement and before the start of each successive fiscal year of the Term, the Parties will agree upon a consistently applied methodology for determining and allocating to Program Costs (including Development Expenses and Sales and Marketing Expenses) for such year an appropriate portion of each of their respective (i) costs and expenses that relate both to the Product and any of the Parties' other products or programs and (ii) G&A Costs and other overhead attributable to this Agreement.

8.8. Audits and Interim Reviews. Each Party will maintain accurate books and records regarding Program Costs, Fully-Absorbed Cost of Goods, External Sales & Marketing Expenses, Internal Sales & Marketing Expenses, External Development Expenses, and Internal Development Expenses, Net Revenues and Net Sales, as applicable, sufficient to enable the calculation of amounts payable hereunder to be verified, and will retain such books and records for each quarterly period for three (3) years after submission of the corresponding report pursuant to this Agreement. Either Party will have the right to request that an independent certified public accountant selected by it (but excluding its own accountant) and reasonably acceptable to the other Party perform an audit, not more than once in any four (4) consecutive Calendar Quarters during the Term, but including one post-termination audit and, if any such audit results in a material restatement of records (*i.e.*, a discrepancy of 5% or more for any calendar year), such Party will be permitted an additional examination within such four (4) quarter period, of the other Party's books of accounts covering the preceding three (3) year period for the sole purpose of verifying compliance with the payment provisions of this Agreement. Such audits will be conducted at the expense of the requesting Party at reasonable times during regular business hours and upon at least twenty (20) business days' prior notice. Audit results will be shared with both Parties, subject to Article 12 (Confidentiality); provided, however, that the accounting firm may not disclose copies of the audited Party's books of accounts (or excerpts thereof) to the other Party. Any accounting firm conducting such an audit will enter into a confidentiality agreement with both Parties containing restrictions substantially similar to the confidentiality provisions of Article 12 (Confidentiality) limiting the disclosure and use of information contained in such books and records for the purposes expressly permitted by this Section 8.8. Any inspection or audit pursuant to this Section 8.8 will be at the expense of the Party initiating the audit; provided, however, that if the Party's accountants reasonably determine that Net Profits or Net Revenues have been understated or Program Costs (including associated labor costs, reimbursable costs and expenses) or Fully-Absorbed Cost of Goods, External Sales & Marketing Expenses, Internal Sales & Marketing Expenses, External Development Expenses, and Internal Development Expenses have been overstated by an amount equal to or greater than five percent (5%), for any calendar year, the audited Party will pay the reasonable fees of such accountants for such audit, in addition to remitting the Net Profits

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

or refund of Net Losses, Program Costs, Fully-Absorbed Cost of Goods, External Sales & Marketing Expenses, Internal Sales & Marketing Expenses, External Development Expenses, or Internal Development Expenses with interest thereon computed in accordance with Section 8.10 (Interest on Late Payments).

8.9. Withholding Taxes. If Applicable Law requires that taxes be withheld from payments made hereunder, or from Net Revenue or Net Profits, the Party making such payments or otherwise responsible for such withholding (the "Withholding Party") will (a) deduct such taxes from any payments to which they relate or in the case of taxes withheld from the other Party's share of Net Revenues or Net Profits account for such taxes as amounts paid on behalf of the other Party, (b) timely pay such taxes to the proper authority and (c) send written evidence of payment to the Party with respect to which such taxes were withheld or paid within sixty (60) days after payment. Taxes withheld from payments made hereunder will be treated as

amounts received by the Party with respect to which such taxes were withheld for all purposes under this Agreement. If the Withholding Party is required to withhold and pay over taxes on the other Party's share of Net Revenues or Net Profits, the other Party will promptly reimburse or otherwise make whole the Withholding Party for any amounts so withheld upon receipt of written evidence of the payment of such taxes. Any taxes paid (excluding income taxes) by the Withholding Party on the other Party's share of Net Revenues or Net Profits for which the Withholding Party has not been reimbursed or otherwise made whole within thirty (30) days after the end of each Reporting Period will be treated as an amount received by the other Party (and not by the Withholding Party) for purposes of determining amounts owed under Section 8.6.2 (Reconciliation). Each Party will assist the other Party or Parties in claiming tax refunds, deductions or credits at such other Party's request and will cooperate to minimize any withholding tax as permitted by Applicable Law.

8.10. Interest on Late Payments. Any 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 (x) 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 one percent (1%) or (y) the maximum rate permissible under applicable law.

8.11. Currency; Payment. All amounts payable under this Agreement will be paid in United States dollars in immediately available funds, and will be directly deposited to a bank account designated for this purpose from time to time by the Party to receive payment. Isis will provide the necessary bank account information to Genzyme no later than the Execution Date and may update such information from time to time by written notice. The Parties may vary the method of payment set forth herein at any time upon mutual agreement, consistent with Applicable Law. As applicable, Net Sales, Net Sales Adjustments, and other elements of Net Revenue and Program Costs will be translated into United States dollars at the exchange rate used by Genzyme for public financial accounting purposes in accordance with GAAP. If, due to restrictions or prohibitions imposed by national or international authority, payments cannot be made as provided in this Article 8 (Financial Provisions) with respect to sales occurring outside of the United States, the Parties will consult with a view to finding a prompt and acceptable solution,

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

and Genzyme will deal with such monies as Isis may lawfully direct.

8.12. Material Safety Warnings. Notwithstanding the financial provisions contained in this Article 8 (Financial Provisions), in the event that the approved label for the Product [**], which is not anticipated by the Parties as of the Effective Date, the Parties will discuss in good faith (without obligation) the extent to which such [**] change the [**] for the Product.

Article 9.
INTELLECTUAL PROPERTY MATTERS

9.1. Product-Specific Patents.

9.1.1. Assignment of Product-Specific Patents. Isis will assign and transfer, and hereby does assign and transfer, to Genzyme, all rights, title, and interests in and to the Product-Specific Patents and all claims and causes of action arising from or relating to the Product-Specific Patents, including all rights to recovery for damages from infringement arising prior to, on or after the Execution Date. Simultaneously with the execution of this Agreement, Isis will execute and deliver a confirmatory assignment relating to all Product-Specific Patents in existence on the Execution Date in the form attached to this Agreement as Exhibit E.

9.1.2. Disclosure of Future Product-Specific Patents. Upon becoming aware of any potentially patentable invention Controlled by Isis that would, if patented, be included within the definition of Product-Specific Patents or Licensed Patents, Isis will promptly disclose such invention to Genzyme in writing in reasonable detail.

9.1.3. Covenants in Support of Assignment. Isis will provide all further cooperation which Genzyme reasonably determines is necessary to accomplish the complete transfer of the Product-Specific Patents and all associated rights to Genzyme, and to ensure Genzyme the full and quiet enjoyment of the Product-Specific Patents including executing and delivering further assignments, consents, releases and other commercially reasonable documentation, and providing good faith testimony by affidavit, declaration, deposition, in-person or other proper means and otherwise assisting Genzyme in support of any effort by Genzyme to establish, perfect, defend or enforce its rights in the Product-Specific Patents through filing and prosecution of Product-Specific Patents, interferences, oppositions, other regulatory proceedings, litigation, or other means. Isis will obtain the cooperation of the individual inventors of any inventions disclosed in the Assigned Product Specific Patents, including (a) obtaining signatures of such inventors on any patent applications or other documentation reasonably necessary to obtain patent protection for such inventions and (b) procuring (at Genzyme's expense) such inventors' good faith testimony by affidavit, declaration, deposition in-person or other proper means in support of Genzyme's efforts in establishing,

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

perfecting, defending or enforcing patent rights to such inventions. To the extent Isis cannot transfer and assign the Product-Specific Patents, or any portion thereof, as of the Execution Date, then Isis will transfer and assign such Product-Specific Patents to Genzyme at its first opportunity to do so and pending such transfer and assignment such Product-Specific Patents will be deemed to be Licensed Patents for the purposes of Section 2.1 (Product License). To the extent further transfer or assignment of the Product-Specific Patents is required or permitted and Isis has not executed and returned to Genzyme the form of assignment reasonably requested by Genzyme within ten

(10) business days of the delivery of such assignment to Isis at the address for notices set forth in Section 14.5 (Notices), then Isis hereby irrevocably appoints Genzyme as its attorney-in-fact with the right, authority and ability to execute and enter into such assignment on behalf of Isis. Isis stipulates and agrees that such appointment is a right coupled with an interest and will survive the unavailability of Isis at any future time.

9.1.4. Grant-Back License. Subject to the terms and conditions of this Agreement, Genzyme hereby grants Isis a non-exclusive, non-transferable license (with no right to sublicense) under the Product-Specific Patents to the extent necessary to perform Isis' obligations under this Agreement and the Supply Agreement.

9.2. Program IP.

9.2.1. Ownership. Unless prohibited by Applicable Law, inventorship and authorship will be determined in accordance with U.S. patent and copyright law. Genzyme will own all Genzyme Program IP . Subject to the terms and conditions of this Agreement including Section 2.1 (Product License) and Section 9.1 (Product-Specific Patents), Isis will own all Isis Program IP, and Isis and Genzyme will jointly own all Joint Program IP. Subject to the terms and conditions of this Agreement including Section 2.1 (Product License), Section 9.1 (Product-Specific Patents), 9.2.3 (No Encumbrances) and Article 3 (Exclusivity), each Party will have the right to practice and license the Joint Program IP without consent of the other Party (where consent is required by law, such consent is deemed hereby granted) and without a duty of accounting to the other Party; provided, however that Isis will not grant a license to a Third Party under Joint Program IP to develop or commercialize any nucleic acid molecule whose primary purpose at the time of the license or primary therapeutic benefit at the time of commercialization is to cause the [**], without Genzyme's prior written consent. Notwithstanding the foregoing, Isis will not be in breach of the preceding sentence if, despite exercising commercially reasonable efforts, it inadvertently licenses Joint Know-How to such a Third Party without Genzyme's prior written consent, unless, prior to Isis disclosing such Joint Know-How to such a Third Party licensee, Genzyme provides Isis with a written summary description of such Joint Know-How that clearly indicates it is Joint Know-How under this Agreement. Subject to the terms and conditions of this Agreement, each Party will cooperate with the other Party's efforts to establish, perfect, defend and

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

enforce its rights in its Program IP in the Territory. This Section 9.2.1 will be subject to the terms and conditions of Section 9.3.2 (Terms of Sharing Arrangement).

9.2.2. Cooperation/Compensation of Employees. Each Party represents and agrees that (a) all of its employees and all of its Affiliates' employees acting under its or its Affiliates' authority in the performance of this Agreement or pursuant to the Product License will be obligated under a binding written agreement or established corporate policy to assign to such Party, or as such Party will direct, all Technology and Patents discovered, made, conceived by such employee as a result of such employee's employment, and (b) both it and its Affiliates have taken all appropriate actions under the Applicable Law in the Territory to ensure proper compensation to any employee for the assignment of such Technology and Patents as contemplated hereunder. In the case of all others acting in the performance of the Development Program or Research Programs or pursuant to the Product License, such as consultants, subcontractors, licensees, sublicensees, outside contractors, clinical investigators, agents, or non-employees working for non-profit academic institutions, such others will also be obligated under an agreement that meets the criteria of the preceding sentences, unless otherwise approved by the Parties. The Parties agree reasonably to undertake to enforce the agreements referenced in this Section 9.2.2 (including, where appropriate, by legal action) considering, among other things, the commercial value of such Technology and Patents.

9.2.3. No Encumbrances. Except as expressly provided in this Agreement, neither Party will sell, transfer, assign, mortgage, pledge, lease, grant a security interest in (*e.g.*, as collateral for a loan or other financing) or otherwise encumber in the Territory any Joint Program IP necessary or useful for the research, development, manufacture or commercialization of the Product in the Territory without the prior written consent of the other Party; provided, however, that nothing contained in this Section 9.2.3 will prohibit an assignment permitted by Section 14.7 (Binding Effect; Assignment) or a license permitted by Section 9.2.1 (Ownership).

9.3. Manufacturing Improvements.

9.3.1. Background. As part of its collaborations with other pharmaceutical partners, Isis has an arrangement where Isis can share manufacturing technology improvements made by such pharmaceutical partners with other third parties so long as such third parties similarly agree to share their manufacturing technology improvements. After reviewing the proposed terms of such arrangement, Genzyme is willing to participate in the arrangement only with the clarifications and under the terms set forth in this Section 9.3 (Manufacturing Improvements).

9.3.2. Terms of Sharing Arrangement.

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

(a) During the period beginning on the Effective Date and ending [**] (the "Sharing Period"), the Parties will meet at least annually to review Manufacturing Improvements developed by either of the Parties during the Sharing Period during and in connection with the conduct of the Development Program or the Research Programs or commercializing the Product and, in the case of Isis, any Manufacturing

Improvements made by or on behalf of Isis or any Participating Isis Partners and disclosed to Isis pursuant to a Sharing Agreement. The Parties will disclose all Manufacturing Improvements Controlled by such Party (including, in the case of Isis, Manufacturing Improvements made by other Participating Isis Partners and disclosed to Isis pursuant to a Sharing Agreement) in reasonable detail as to enable the other Party to use such Manufacturing Improvements in the manufacture of ASO Products. All such disclosures will be subject to appropriate confidentiality obligations. Isis will have the right to disclose and sublicense any Manufacturing Improvements Controlled by Genzyme only to Third Parties that are licensees of Isis with respect to the commercialization of one or more ASO Products and are Participating Isis Partners and only in accordance with Section 9.3.2(b).

(b) Without limiting the generality of Section 9.2.1 (Ownership), all rights, title, and interests in and to all Manufacturing Improvements developed or invented during the Sharing Period during and in connection with the conduct of the Development Program or the Research Programs or commercializing the Product solely by Genzyme's employees or Third Parties acting on Genzyme's behalf ("Genzyme Manufacturing Improvements") will be the sole and exclusive property of Genzyme. Genzyme hereby grants Isis a worldwide, royalty-free, perpetual, non-exclusive license to practice under Genzyme's rights to any Know-How in or Patent Covering such Genzyme Manufacturing Improvements Controlled by Genzyme to make and have made ASO Products other than the Product. The license granted under this Section 9.3.2(b) is sublicensable by Isis to Participating Isis Partners solely in connection with a license to develop, make, use, import, offer for sale and sell an ASO Product developed or commercialized by a Participating Isis Partner. Such Participating Isis Partners may not further disclose or sublicense Genzyme Manufacturing Improvements except in connection with a sublicense of the ASO Product being developed or commercialized under license from Isis. The license granted under this Section 9.3.2(b) will survive the termination of this Agreement with respect to any Genzyme Manufacturing Improvements made prior to such termination.

(c) Without limiting the generality of Section 9.2.1 (Ownership), all rights, title, and interests in and to all Manufacturing Improvements developed or invented during the Sharing Period solely by Isis's employees or Third Parties acting on Isis' behalf ("Isis Manufacturing Improvements") will be the sole and exclusive property of Isis. Without limiting the rights granted to Genzyme in Article 2, Isis hereby grants Genzyme a worldwide, royalty-free, perpetual, non-exclusive license to practice under Isis' rights to any Know-How in or Patent Covering any Manufacturing Improvements Controlled by Isis (including any

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

Manufacturing Improvements made by or on behalf of any Participating Isis Partners) to make and have made the Product and other ASO Products developed or commercialized by Genzyme. The license granted under this Section 9.3.2(c) is sublicensable by Genzyme solely in connection with a license to develop, make, use, import, offer for sale and sell an ASO Product developed or commercialized by Genzyme under license from Isis (including the Product). The license granted under this Section 9.3.2(c) will survive the termination of this Agreement or any Sharing Agreement with respect to any Manufacturing Improvements (including any Manufacturing Improvements made by Participating Isis Partners) made prior to such termination.

(d) Notwithstanding Section 9.2.1 (Ownership) and subject to Section 9.1 (Product-Specific Patents), all rights, title, and interests in and to all Manufacturing Improvements developed or invented during the Sharing Period jointly by Isis' and Genzyme's employees or Third Parties acting on Isis' and Genzyme's behalf will be the joint property of Isis and Genzyme with each party having an undivided joint interest in such Manufacturing Improvements. Each Party may license its rights under such Manufacturing Improvements for its own account and without the consent of the other Party (where consent is required by law, such consent is deemed hereby granted) and without a duty of accounting to the other Party, subject in all cases to the licenses granted to Genzyme under Article 2 (Licenses).

9.3.3. [**].

9.3.4. [**] Manufacturing Improvements. If Isis does not [**] of the Execution Date, Isis will [**]. In such event, Isis will be solely responsible for all costs and expenses associated with such development effort and will reimburse Genzyme for any such costs and expenses incurred by Genzyme. Failure of Isis to reimburse Genzyme for such costs and expenses will be deemed to be a material breach of this Agreement entitling Genzyme to setoff such amounts pursuant to Section 11.4.2 (Genzyme's Right of Setoff).

9.3.5. Representations Regarding [**]. Isis represents and warrants to Genzyme as follows:

(a) [**], Isis will Control all Know-How [**] that is [**] the manufacture, development or commercialization of Mipomersen, including the [**] Manufacturing Improvements and will have the sufficient legal and/or beneficial title and ownership or rights to grant the Product License to Genzyme under such Know-How and the grant of such license to Genzyme does not violate the terms of any Third Party Agreement or any other agreement Isis has with a Third Party [**].

(b) If [**], Isis will Control all Know-How [**] that is [**] the manufacture, development or commercialization of Mipomersen as of such date and will have

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

the sufficient legal and/or beneficial title and ownership or rights to grant the Product License to Genzyme under such Know-How and the grant of such license to Genzyme does not violate the terms of any Third Party Agreement or any other agreement Isis has with a Third

[**].

9.3.6. [**] Sharing Agreement. Isis will use reasonable efforts to [**].

9.3.7. Cooperation. Genzyme will provide reasonable cooperation with Isis' efforts to [**]. In no event, however, will Genzyme be required to enter into any agreement that (i) [**] in any way or (ii) imposes any material obligations, liabilities or constraints on Genzyme except those contemplated by this Agreement.

9.4. Filing, Prosecution and Maintenance of Patents.

9.4.1. Responsibility.

(a) Product-Specific Patents and Genzyme Program Patents. Genzyme, through counsel of its choosing and at its sole expense, will be responsible for and have control over obtaining, prosecuting (including any interferences, reissue proceedings, re-examinations and oppositions), and maintaining throughout the Territory the Product-Specific Patents and Genzyme Program Patents in Genzyme's name and Isis will cooperate with Genzyme in regard thereto. Without limiting the generality of the foregoing, Genzyme may, in its sole discretion, elect not to pursue patent protection for any Product-Specific Patent(s) and Genzyme Program Patent(s) in one or more countries in the Territory. Genzyme will consider input from the JPC regarding prosecution strategy for the Product-Specific Patents and Genzyme Program Patents, but will make all decisions relating to the prosecution and maintenance of Product-Specific Patents and Genzyme Program Patents.

(b) Licensed Product Patents.

(i) Primary Responsibility. Subject to Section 9.4.2(a) (Election Not to Continue Prosecution; Abandonment) and this Section 9.4.1(b), Genzyme, through counsel of its choosing and at its sole expense, will have primary responsibility for and control over obtaining, prosecuting (including any interferences, reissue proceedings, re-examinations and oppositions), and maintaining throughout the Territory the Licensed Product Patents and Isis will cooperate with Genzyme in regard thereto; provided, however that Genzyme will prosecute such Licensed Product Patents such that they do not claim (x) [**] other than apoB, or (y) methods of using such nucleic acids as a therapeutic or [**] other than apoB. Genzyme will consider input from Isis regarding prosecution strategy for the Licensed Product Patents, but will make all decisions relating to the prosecution and maintenance of Licensed Product Patents.

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

(ii) Prosecution Strategy. In prosecuting Licensed Product Patents, the Parties will avoid filing patent applications that both claim (a) [**] apoB, (b) the [**] of apoB, (c) the specific composition of matter of a Product, or (d) methods of using Product as a therapeutic, methods of using Product to modulate apoB, or methods of using the Product to inhibit expression of apoB, and also claim (x) [**] other than apoB, or (y) methods of using such nucleic acids as a therapeutic or [**] other than apoB.

(c) Isis Core Technology Patents and the Isis Manufacturing and Analytical Patents. Subject to Section 9.4.2(b) (Election Not to Continue Prosecution; Abandonment), Isis, through counsel of its choosing and at its sole expense, will have primary responsibility for and control over obtaining, prosecuting (including any interferences, reissue proceedings, re-examinations and oppositions), and maintaining throughout the Territory the Isis Core Technology Patents and the Isis Manufacturing and Analytical Patents (in each case, other than Joint Patents), and Genzyme will cooperate with Isis in regard thereto. Isis will consider input from the JPC regarding prosecution strategy for the Isis Core Technology Patents, Isis Manufacturing and Analytical Patents (in each case, other than Joint Patents) and will consult with Genzyme before taking any action that would have an adverse impact on the scope of claims within the Special Isis Core Technology Patents (other than Joint Patents). However, Isis will make all decisions relating to the prosecution and maintenance of the Isis Core Technology Patents and Isis Manufacturing and Analytical Patents (in each case, other than Joint Patents). For clarity, this Section 9.4.1(c) will not apply to Joint Patents that are Isis Core Technology Patents or Isis Manufacturing and Analytical Patents, which will be governed Section 9.4.1(d) below.

(d) Joint Patents. Subject to Section 9.4.1(a) (Product-Specific Patents and Genzyme Program Patents) and Section 9.4.1(b) (Licensed Product Patents), with respect to any Joint Patent (other than Product-Specific Patents and Licensed Product Patents), the JPC will designate one Party (the "Responsible Party") who will have primary responsibility for the preparation, filing, prosecution and maintenance of any such Joint Patent in the Territory (in both Genzyme's and Isis' name), using patent counsel selected by the JPC or otherwise agreed by the Parties. If the JPC has disbanded, the Parties will mutually agree on a Responsible Party. Each Party will assist the Responsible Party in the preparation, filing, prosecution and maintenance of such Joint Patents. The Responsible Party will consult with and keep the other Party (through the JPC if possible) informed of important issues relating to the preparation, filing, prosecution and maintenance of the Joint Patents (other than Product-Specific Patents or Licensed Product Patents) and will furnish the other Party (through the JPC if possible) with copies of documents relevant to such preparation, filing, prosecution or maintenance in sufficient time prior to filing such document or making any payment due thereunder to allow for review and comment by the other Party and, to the extent possible in the reasonable exercise of its discretion,

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

the Responsible Party will incorporate all such comments. If the Responsible Party decides to discontinue the preparation, filing, prosecution or maintenance of a Joint Patent (other than a Product-Specific Patent or Licensed Product Patent), the Responsible Party will notify the other Party at least sixty (60) days prior to any deadline that, if missed, would materially prejudice the Joint Patent, and the other Party will have the right to prepare, file, prosecute and maintain such Patent. The Parties will share equally the reasonable costs and expenses of the preparation, filing, prosecution and maintenance of such Joint Patents (other than Product-Specific Patents and Licensed Product Patents), and such costs and expenses will be considered Program Costs. Neither Party will make any statements or omissions or take any other action during prosecution or enforcement of any Joint Patent (other than Product-Specific Patents and Licensed Product Patents) which admits or concedes that any of the Licensed Patents (or any Product-Specific Patent) is invalid or unenforceable, which adversely affects or limits the scope of any claims in any such Patent, or which adversely affects the other Party's rights under this Agreement in any way, without the prior written consent of the other Party. For clarity, this Section 9.4.1(d) does not apply to Joint Patents that are Product-Specific Patents or Licensed Product Patents, which are governed by Section 9.1 (Product-Specific Patents) and Section 9.4.1(a) and Section 9.4.1(b) above, but does apply to Joint Patents that are Isis Core Technology Patents or Isis Manufacturing and Analytical Patents.

9.4.2. Election Not to Continue Prosecution; Abandonment.

(a) If Genzyme elects not to file for or continue the prosecution (including any interferences, oppositions, reissue proceedings and re-examinations) or maintenance of a Licensed Product Patent in a particular country in the Territory, then Genzyme will notify Isis promptly in writing of its intention in good time to enable Isis to meet any deadlines by which an action must be taken to establish or preserve any such rights in such Patent in such country and Isis will have the right, but not the obligation, to file for or continue the prosecution or maintenance of such Patent in such country, and Genzyme will cooperate with Isis in regard thereto. In such event, Isis' expenses incurred in connection with the prosecution or maintenance of such Patent in such country will be Program Costs.

(b) If Isis elects not to file for or continue the prosecution (including any interferences, oppositions, reissue proceedings and re-examinations) or maintenance of a Special Isis Core Technology Patent (other than Joint Patents), then, Isis will notify Genzyme promptly in writing of its intention in good time to enable Genzyme to meet any deadlines by which an action must be taken to establish or preserve any such rights in such Patent in such country and Genzyme will have the right, but not the obligation, to file for or continue the prosecution or maintenance of such Patent in such country, and Isis will cooperate with Genzyme in regard thereto. In such event, Genzyme's expenses incurred in connection with the prosecution or maintenance of such Patent in such country will be Program Costs. For clarity, this Section 9.4.2(b) will not apply to Joint

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

Patents that are Special Isis Core Technology Patents, which will be governed Section 9.4.1(d) (Joint Patents).

9.4.3. Cooperation. Each Party hereby agrees: (a) to make its employees, agents and consultants reasonably available to the other Party (or to the other Party's authorized attorneys, agents or representatives), to the extent reasonably necessary to enable such Party to undertake patent prosecution as contemplated by this Agreement; (b) to cooperate, if necessary and appropriate, with the other Party in gaining patent term extensions wherever applicable to Patents that are subject to this Agreement; and (c) to endeavor in good faith to coordinate its efforts with the other Party to minimize or avoid interference with the prosecution and maintenance of the other Party's patent applications that are subject to this Agreement.

9.5. Enforcement of Patents and Know-How.

9.5.1. Notification. Each Party will promptly report in writing to the other Party during the Term any (a) known or suspected Third Party infringement of any Product-Specific Patents, Licensed Product Patents, Special Isis Core Technology Patent, or (b) known or suspected Third Party infringement of any Isis Core Technology Patents or Isis Manufacturing and Analytical Patents to the extent the infringement relates to a product that contains a nucleic acid that hybridizes to a nucleic acid molecule encoding apoB, or (c) unauthorized use or misappropriation of any Product Know-How or other Confidential Information by a Third Party of which it becomes aware, and will provide the other Party with all available evidence supporting such infringement or unauthorized use or misappropriation.

9.5.2. Rights to Enforce.

(a) Genzyme First Right. Genzyme will have the first right, but not the obligation, to take any reasonable measures it deems appropriate to stop activities in the Territory infringing the Product-Specific Patents, Licensed Product Patents or the use without proper authorization of any Product Know-How or the infringement of any Isis Core Technology Patent by a Third Party product that contains a [**] encoding apoB, including (i) initiating or prosecuting an infringement or other appropriate suit or action against or (ii) granting adequate rights and licenses necessary for continuing such activities in the Territory to any Third Party who at any time has infringed, or is suspected of infringing, any Product-Specific Patents or Licensed Product Patents or has used or is suspected of using without proper authorization the Product Know-How. If Genzyme desires to assert an Isis Core Technology Patent pursuant to this Section 9.5.2(a) and the infringing product is also Covered by a Product-Specific Patent, then Genzyme will assert both the Product-Specific Patent and the Isis Core Technology Patent, unless it obtains Isis' written consent to assert only the Isis Core Technology Patent. In such a case, at Genzyme's request Isis' representatives will meet with Genzyme's representatives to discuss whether it

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

would be advisable to assert an Isis Core Technology Patent without also asserting a Product-Specific Patent.

(b) Isis First Right. Subject to Section 9.5.2(a) (Genzyme First Right to Enforce), Isis will have the first right, but not the obligation, to take any reasonable measures it deems appropriate to stop activities in the Territory infringing the Isis Core Technology Patents or Isis Manufacturing and Analytical Patents (in each case, other than Joint Patents) or the use without proper authorization of any Isis Manufacturing and Analytical Know-How (other than Joint Know-How), including (i) initiating or prosecuting an infringement or other appropriate suit or action against or (ii) granting a Permitted License to any Third Party who at any time has infringed, or is suspected of infringing, any Isis Core Technology Patents or Isis Manufacturing and Analytical Patents (other than Joint Patents) or has used or is suspected of using without proper authorization the Isis Manufacturing and Analytical Know-How (other than Joint Know-How). For clarity, this Section 9.5.2(b) will not apply to Joint Patents that are Isis Core Technology Patents or Isis Manufacturing and Analytical Patents, which will be governed Section 9.5.2(c) (Joint Patents and Know-How).

(c) Joint Patents and Know-How. Subject to Section 9.5.2(a) (Genzyme First Right to Enforce), Isis and Genzyme will confer and may agree jointly to take any reasonable measures they deem appropriate to stop activities in the Territory infringing the Joint Patents (other than Product-Specific Patents and Licensed Product Patents) or the use without proper authorization of any Joint Know-How and any expenses of taking such measures will be included as Program Costs. If the Parties do not agree on whether or how to proceed with enforcement activity within either (i) sixty (60) days following the notice of alleged infringement or (ii) ten (10) days before the time limit to respond, if any, set forth in the Applicable Law for the filing of such actions, whichever comes first, then either Party may commence litigation with respect to the alleged or threatened infringement at its own expense. In the event a Party brings an infringement action, the other Party will cooperate reasonably at the litigating Party's expense, including being joined as a party-plaintiff and providing good faith testimony. The other Party will have the right, at its expense, to retain its own counsel to monitor such litigation, and the costs associated with such monitoring will not be Program Costs. Neither Party will have the right to settle any patent infringement or Know-How misappropriation litigation under this Section in a manner that diminishes the rights or interests of the other Party without the express written consent of such other Party. For purposes of clarification, the grant of a license under a Joint Patent to a Third Party that would not otherwise result in a breach under this Agreement will not be considered to diminish the rights or interests of the other Party. Notwithstanding the foregoing, this Section 9.5.2(c) will not apply to Joint Patents that are Product-Specific Patents or Licensed Product Patents or to the infringement of any Joint Patent that is a Isis Core Technology Patent by a Third Party product that [**] encoding apoB, each of which will be governed by Section 9.5.2(a) (Genzyme First Right to Enforce) above.

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

9.5.3. Election Not to Enforce.

(a) Isis Second Right. In the event that Genzyme elects not to take action pursuant to Section 9.5.2(a) (Genzyme First Right to Enforce), Genzyme will so notify Isis in writing of its intention within ninety (90) days of Genzyme's notice of such infringement activities to enable Isis to meet any deadlines by which an action must be taken to establish or preserve any enforcement rights, and Isis will have the right, but not the obligation, to take any such reasonable measures to stop such infringing activities by such alleged infringer. Notwithstanding the foregoing, Genzyme will have the *exclusive* right to bring actions with respect to infringement of Product-Specific Patents or Licensed Product Patent. Accordingly, Genzyme will not be required to notify Isis with respect to any election not to take action with respect to a Product-Specific Patent, and Isis will have no right to take reasonable measure to stop any infringement of Product-Specific Patents.

(b) Genzyme Second Right. In the event that Isis elects not to take action pursuant to Section 9.5.2(b) (Isis First Right to Enforce), Isis will so notify Genzyme in writing of its intention within ninety (90) days of Isis' notice of such infringement activities to enable Genzyme to meet any deadlines by which an action must be taken to establish or preserve any enforcement rights, and Genzyme will have the right, but not the obligation, to take any such reasonable measures to stop any such infringing activities that involves a product that causes the [**]. If Genzyme desires to assert an Isis Core Technology Patent pursuant to this Section 9.5.3(b) and the infringing product is also Covered by a Product-Specific Patent, then Genzyme will assert both the Product-Specific Patent and the Isis Core Technology Patent, unless it obtains Isis' written consent to assert only the Isis Core Technology Patent.

(c) Due Consideration. In any event, if one Party has elected not to take action pursuant to Section 9.5.2 (Right to Enforce), then it will explain its reasons for such decision to the other Party, and the other Party will consider these reasons in good faith prior to determining whether to exercise its second right to take action.

9.5.4. Procedures and Expenses.

(a) The Party having the right to initiate any infringement suit under Section 9.5.2 (Rights to Enforce) or Section 9.5.3 (Election Not to Enforce) above will have the sole and exclusive right to select counsel for any such suit and will pay all expenses of the suit, including attorneys' fees and court costs and reimbursement of the other Party's reasonable out-of-pocket expenses in rendering assistance requested by the initiating Party. If required under Applicable Law in order for the initiating Party to initiate and/or maintain such suit, or if either Party is unable to initiate or prosecute such suit solely in its own name or it is otherwise advisable to obtain an effective legal remedy, in each case,

the other Party will join as a party to the suit and will execute and cause its Affiliates to execute all documents necessary for the initiating Party to initiate litigation to prosecute and maintain such action. In addition, at the initiating Party's request, the other Party will provide reasonable assistance to the initiating Party in connection with an infringement suit at no charge to the initiating Party except for reimbursement by the initiating Party of reasonable out-of-pocket expenses incurred in rendering such assistance. The non-initiating Party will have the right to participate and be represented in any such suit by its own counsel at its own expense.

(b) If the Parties have mutually agreed that a Party should initiate an infringement action or take such other reasonable measures it deems appropriate to stop infringing activities under Section 9.5.2 (Rights to Enforce) or Section 9.5.3 (Election Not to Enforce), then any expenses incurred by such Party to take such action will be included in Program Costs.

9.5.5. Recoveries. If the Parties obtain from a Third Party infringer, in connection with such suit, any damages, license fees, royalties or other compensation (including any amount received in settlement of such litigation), such amounts will be allocated as follows:

(a) If the Parties mutually agreed that such Third Party infringer should be pursued under Section 9.5.2 (Rights to Enforce) or Section 9.5.3 (Election Not to Enforce) and the expenses incurred in connection with such action were included in Program Costs, then any amounts recovered by either Party will be included as Net Revenues. In such case, the Party pursuing the Third Party infringer under Section 9.5.2 or 9.5.3 will bear all payments awarded against or agreed to be paid by such Party pursuant to such action, including any costs or expenses incurred that exceed the amounts recovered by such Party, but such payments, costs and expenses will be included as Program Costs.

(b) If the Parties did not mutually agree that such Third Party infringer should be pursued under Section 9.5.2 (Rights to Enforce) or Section 9.5.3 (Election Not to Enforce) and the expenses incurred in connection with such action were not included in Program Costs, then any amounts recovered by either Party will be used to reimburse the Parties for their reasonable costs and expenses, including attorneys' fees incurred in making such recovery (which amounts will be allocated pro rata if insufficient to cover the totality of such expenses), with any remainder to be retained by the Party initiating action under Section 9.5.2 (Rights to Enforce) or Section 9.5.3 (Election Not to Enforce). In such case, such initiating Party will bear all payments awarded against or agreed to be paid by such Party pursuant to such action, including any costs or expenses incurred that exceed the amounts recovered by such Party, and such payments will not be included as Program Costs.

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

9.6. Claimed Infringement of Third Party Rights.

9.6.1. Notice. In the event that a Third Party at any time provides written notice of a claim to, or brings an action, suit or proceeding against, any Party, or any of such Party's respective Affiliates or sublicensees, claiming infringement of its patent rights or unauthorized use or misappropriation of its know-how, based upon the development, manufacture or commercialization of the Product in the Territory ("Infringement Claim"), such Party will promptly notify the other Party of the Infringement Claim or the commencement of such action, suit or proceeding, enclosing a copy of the Infringement Claim and all papers served. Each Party agrees to make available to the other Party its advice and counsel regarding the technical merits of any such claim at no cost to the other Party and to offer reasonable assistance to the other Party at no cost to the other Party.

9.6.2. Defense of Infringement Claim; Declaratory Judgment Actions.

(a) Genzyme will have the first right, but not the obligation, to control the defense of any Infringement Claim brought against either Party or any of its Affiliates or sublicensees arising out of the development, manufacture or commercialization of the Product in the Territory. Isis will have the second right, but not the obligation to control the defense of an Infringement Claim in the event Genzyme fails to exercise its right to assume such defense within thirty (30) days following written notice from the other Party of such Infringement Claim. In addition, if applicable prior to the initiation of an Infringement Claim, Genzyme will have the *exclusive* right, but not the obligation, to bring a declaratory judgment action relating to any Patent that a Third Party has alleged is infringed by the development, manufacture or commercialization of the Product in the Territory. Genzyme will not settle any such claims or suits in a manner that admits the invalidity or unenforceability of any Isis Core Technology Patent or Isis Manufacturing and Analytical Patent or that agrees to any injunction or other equitable remedy binding Isis without obtaining the prior written consent of Isis. Similarly, Isis will not settle any such claims or suits in a manner that admits the invalidity or unenforceability of any Product-Specific Patent or Licensed Product Patent or that agrees to any injunction or other equitable remedy binding Genzyme without obtaining the prior written consent of Genzyme. All litigation costs and expenses incurred in connection with such Infringement Claim or declaratory judgment action, and all damages, payments and other amounts awarded against, or payable by, either Party, including under any settlement with such Third Party, will be included as Program Costs.

(b) The Party controlling the defense of an Infringement Claim or bringing such declaratory judgment action will have the sole and exclusive right to select counsel for any Infringement Claim; provided, however, that it will consult with the other Party with respect to selection of counsel for such defense. The Party controlling the defense of an Infringement Claim or bringing such declaratory judgment action will keep the other Party informed, and will from time to time

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

consult with the other party regarding the status of any such claims and will provide the other party with copies of all documents filed in, and all written communications relating to, any suit brought in connection with such claims. The other Party will also have the right to participate and be represented in any such claim or related suit, at its own expense.

9.6.3. Other Challenges. If the JPC determines (or if after the JPC disbands, the Parties mutually agree) that a Patent owned by a Third Party is or could potentially or arguably be infringed by the development, manufacture or commercialization of the Product in the Territory, then the Parties will discuss the matter and agree upon a strategy relating to such Third Party Patent; provided, however, that if the Parties fail to agree upon such a strategy, then subject to Section 9.3 (Filing, Prosecution and Maintenance of Patents) and Section 9.5 (Enforcement of Patents and Know-How), Genzyme will determine the appropriate strategy in its reasonable discretion. If, consistent with such strategy, either or both Parties challenge such Third Party Patent through opposition, re-examination, nullity or revocation proceeding, or other available administrative mechanism, then all costs and expenses incurred by the Parties in connection with such challenge will be included as Program Costs.

9.7. Other Infringement Resolutions. In the event of a dispute or potential dispute that has not ripened into a demand, claim or suit of the types described in Section 9.5 (Enforcement of Patents and Know-How) and Section 9.6 (Claimed Infringement of Third Party Rights) (*e.g.*, actions seeking declaratory judgments and revocation proceedings), the same principles governing control of the resolution of the dispute, consent to settlements of the dispute, and implementation of the settlement of the dispute (including sharing in and allocating the payment or receipt of damages, license fees, royalties and other compensation) will apply. Each Party will immediately notify the other Party of any certification of which it becomes aware filed pursuant to 21 U.S.C. § 355(b)(2)(A) or § 355(j)(2)(A)(vii) (or any amendment or successor statute thereto) or declaratory judgment action filed by a Third Party claiming that a Product-Specific Patent, Licensed Product Patent, Special Isis Core Technology Patent is invalid or that infringement of such Patent will not arise from the development, manufacture, use or sale of any product by a Third Party. The provisions of Section 9.5 (Enforcement of Patents and Know-How) will thereafter apply as if such Third Party were an infringer or suspected infringer; provided, however, that in the event that Genzyme elects not to take action, Genzyme will so notify Isis in writing of its intention within ten (10) days of Genzyme's notice of such infringement activities to enable Isis to meet any deadlines by which an action must be taken to establish or preserve any enforcement rights.

9.8. Patent Term Extensions. The Parties will use commercially reasonable efforts to obtain all available supplementary protection certificates ("SPC") and other extensions of Licensed Patents and Product-Specific Patents (including those available under the Hatch-Waxman Act). The Parties will cooperate with each other in gaining patent term restorations, extensions and/or SPCs wherever applicable to Licensed Patents and Product-Specific Patents. If more than one patent is eligible for extension or patent term

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

restoration, Genzyme will determine, in its sole discretion, a strategy that will be designed to maximize patent protection and commercial value for the Product, and the Parties will seek patent term restorations in accordance with that strategy. The Party who is responsible under this Agreement for prosecution and maintenance of the relevant Patent will make the filings for such extensions and certificates as directed by Genzyme. Each Party will execute such authorizations and other documents and take such other actions as may be reasonably requested by the other Party to obtain such extensions.

9.9. Orange Book Listings. At least fifteen (15) business days prior to the expiration of the time period under 21 C.F.R. § 314.53, or any successor regulation, for submitting patent information pertaining to Product-Specific Patents, Licensed Product Patents, Isis Core Technology Patents or Isis Manufacturing and Analytical Patents with respect to the Product, Genzyme will submit to Isis any such draft submission, including any forms such as Form FDA 3542, Form FDA 3542a or any equivalent thereof, for Isis' review and comment. Genzyme will consider in good faith any comments made by Isis pursuant to this Section. In the event that the Parties, after good faith discussions, cannot agree with respect to any decision to be made concerning such submission of patent information, Genzyme will make such decision.

9.10. Cooperative Research and Technology Act Acknowledgement. The Parties acknowledge and agree that this Agreement is a joint research agreement for the purposes of Section 35 U.S.C. 103(c).

9.11. Common Interest. All information exchanged between the Parties representatives regarding the preparation, filing, prosecution, maintenance, or enforcement of the Product-Specific Patents and Licensed Patents will be deemed Confidential Information. In addition, the Parties acknowledge and agree that, with regard to such preparation, filing, prosecution, maintenance, and enforcement of the Product-Specific Patents and Licensed Patents, the interests of the Parties as collaborators and licensor and licensee are to obtain the strongest patent protection possible, and as such, are aligned and are legal in nature. The Parties agree and acknowledge that they have not waived, and nothing in this Agreement constitutes a waiver of, any legal privilege concerning the Product-Specific Patents and the Licensed Patents, including privilege under the common interest doctrine and similar or related doctrines.

9.12. Product Trademarks. Genzyme will select and own the Product Trademarks for the Product and will be solely responsible for applying for and maintaining registrations the Product Trademarks in the Territory (including payment of costs associated therewith), and all goodwill associated therewith will inure to the benefit of Genzyme. All costs incurred by Genzyme to apply for and maintain Product Trademarks, will be included as Program Costs. Genzyme will assume full responsibility, at its sole cost and expense, for any infringement of a Product Trademark by a Third Party,

and will defend and indemnify Isis for and against any claims of infringement of the rights of a Third Party by the use of a Product Trademark in connection with the Product in accordance with Section 10.3 (Indemnification).

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

Article 10.
REPRESENTATIONS AND WARRANTIES; INDEMNIFICATION

10.1. Representations and Warranties of Both Parties. Each Party hereby represents and warrants to the other Party as of the Execution Date that:

10.1.1. it is a duly organized and validly existing corporation under the laws of its jurisdiction of incorporation;

10.1.2. it has the power and authority and the legal right to enter into this Agreement and perform its obligations hereunder, and that it has taken all necessary action on its part required to authorize the execution and delivery of this Agreement and the performance of its obligations hereunder;

10.1.3. the execution and delivery of this Agreement and the performance of such Party's obligations hereunder do not conflict with or violate any requirement of Applicable Law or any provision of its articles of incorporation or similar organizational documents, its bylaws, or the terms or provisions of any agreement or other instrument to which it is a party or by which it is bound, or any order, award, judgment or decree to which it is a party or by which it is bound; and

10.1.4. this Agreement has been duly executed and delivered on behalf of such Party and constitutes a legal, valid and binding obligation of such Party and is enforceable against it in accordance with its terms subject to the effects of bankruptcy, insolvency or other laws of general application affecting the enforcement of creditor rights and judicial principles affecting the availability of specific performance and general principles of equity, whether enforceability is considered a proceeding at law or equity.

10.2. Isis' Representations and Warranties. Isis represents and warrants to Genzyme that the statements contained in this Section 10.2 are true and correct as of the Execution Date with each such representation and warranty subject only to such exceptions, if any, as are set forth in the particular section in the Disclosure Schedule attached hereto as Exhibit F that corresponds to the particular section number in this Agreement:

10.2.1. Schedule 1.52, Schedule 1.56 and Schedule 1.99 set forth true, correct and complete lists of all Isis Core Technology Patents, Isis Manufacturing and Analytical Patents, and Product-Specific Patents, respectively, and all Licensed Patents used in the development or commercialization of Mipomersen and existing as of the Execution Date 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.

10.2.2. A true, correct and complete list of any Third Party Agreements related to Mipomersen and a true and accurate calculation of the royalty burden for Mipomersen (as it exists on the Execution Date) is set forth on Schedule 10.2.2.

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

10.2.3. With respect to the Licensed Patents and all Know-How that is developed by Isis or received by Isis under an agreement with a Third Party that is used in the development or commercialization of Mipomersen [**], Isis has the sufficient legal and/or beneficial title and ownership or rights to grant the Product License to Genzyme under such Licensed Patents and Know-How and the grant of such license to Genzyme does not violate the terms of any Third Party Agreement or any other agreement Isis has with a Third Party.

10.2.4. Isis exclusively owns all rights, title, and interests in, and has good and marketable title to, (a) the Product-Specific Patents and the [**]Patent (b) any other Patent identified on Schedule 1.52 or Schedule 1.56 as being owned by Isis, free of any lien, encumbrance, restriction, or other right or interest granted to any Third Party. Isis owns or Controls all Know-How developed by Isis or received by Isis under an agreement with a Third Party that is used in the development or commercialization of Mipomersen [**].

10.2.5. Each of the Product-Specific Patents, and each of the Licensed Patents used in the development or commercialization of Mipomersen properly identifies each and every inventor of the claims thereof as determined in accordance with the laws of the jurisdiction in which such Patent is issued or such application is pending.

10.2.6. With respect to all Product-Specific Patents owned by Isis, and all Licensed Patents owned by Isis and used in the development or commercialization of Mipomersen, (a) each person who has or has had any rights in or to each of such Patents has executed an agreement assigning his, her or its entire right, title and interest in and to such Patents to Isis and (b) to the best of Isis' knowledge, each such inventor has complied in all material respects with all applicable duties of candor and good faith in dealing with any patent office, including the duty to disclose to any applicable patent office all information known to be material to patentability.

10.2.7. To the best of Isis' knowledge, no circumstances or grounds exist that would invalidate, reduce or eliminate, in whole or in part, the enforceability, validity or scope of any Product-Specific Patent or any Licensed Patent used in the development or commercialization of Mipomersen.

10.2.8. Isis is not aware of any Patents or Know-How owned or Controlled by a Third Party that would be infringed by Genzyme during the development or commercialization of Mipomersen in its current form. To the best of Isis' knowledge, Isis has not misappropriated from any Third Party any Know-How used in the development or commercialization of Mipomersen.

10.2.9. To the best of Isis' knowledge, no actions, suits, claims, disputes or proceedings concerning the Licensed Patents are currently pending or are threatened, that if determined adversely to Isis would have a material adverse effect on or would impair Genzyme's rights under the Product License.

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

10.2.10. Isis is not subject to any agreement with any Third Party or to any outstanding order, judgment or decree of any court or administrative agency that restricts it in any way from granting to Genzyme the Product License.

10.2.11. Isis has not granted, or permitted to be attached, and it will not grant or permit to be attached, any lien, security interest or other encumbrance with respect to any Product-Specific Patent, or any Licensed Patent or Know-How used in the development or commercialization of Mipomersen which would adversely affect the rights granted to Genzyme hereunder.

10.2.12. Each Third Party Agreement related to Mipomersen is in full force and effect, and Isis, and to the best of Isis' knowledge, each counterparty thereto, is in compliance in all material respects with all such Third Party Agreements and no circumstances or grounds exist that would reasonably be expected to give rise to a claim of material breach or right of rescission, termination, revision or amendment of such Third Party Agreements.

10.2.13. Isis has not assigned, licensed, sublicensed, granted any interest in or options to, or entered into an agreement with respect to the Licensed IP with a Third Party that would adversely impair Genzyme's exclusive rights under this Agreement, except for the agreements identified on Schedule 2.1.

10.2.14. Isis has not received any claim alleging that Isis' development of Mipomersen or use of any Product-Specific Patent or any Licensed Patent or Know-How used in the development or commercialization of Mipomersen interferes with, infringes, or misappropriates any intellectual property rights of any Third Party (including any claim that Isis must license or refrain from using any intellectual property rights of any Third Party in order to develop, make, use, sell or offer for sale Mipomersen or any product or technology using or incorporating the Licensed IP), and to the best of Isis' knowledge, the development and commercialization of Mipomersen and the use of any Product-Specific Patent or any Licensed IP used in the development or commercialization of Mipomersen will not interfere with, infringe or misappropriate the intellectual property rights of any Third Party. To the best of Isis' knowledge, no Third Party has interfered with, infringed upon or misappropriated the Licensed IP in the making, using or selling of a lipid lowering product.

10.2.15. Isis holds, and is operating in material compliance with, such exceptions, permits, licenses, franchises, authorizations and clearances of any governmental entity required in connection with the current development of Mipomersen. Isis has not received any warning letters or written correspondence from any governmental entity requiring the termination, suspension or modification of any clinical or pre-clinical studies or tests with respect to Mipomersen. Isis has conducted and required its contractors to conduct all clinical studies related to Mipomersen in accordance with cGCP, cGLP and Applicable Law.

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

10.2.16. As of the Execution Date, Isis has prepared, maintained and retained all Regulatory Materials required to be maintained or reported pursuant to and in accordance with Applicable Law and the Regulatory Materials do not contain any materially false or misleading statements.

10.2.17. Except for the agreements identified on Schedule 2.1, Isis has not granted to any Third Party rights under the Licensed IP to research, develop or commercialize any nucleic acid that hybridizes to a nucleic acid molecule encoding apoB.

10.3. Indemnification.

10.3.1. Indemnification by Genzyme. Genzyme will indemnify, hold harmless, and defend Isis, its Affiliates, and their respective directors, officers, employees and agents ("Isis Indemnitees") from and against any and all action, losses, liabilities, damages, costs, fees and expenses (including reasonable attorneys' fees) arising from a claim, suit, proceeding or other action of a Third Party (collectively, "Losses") arising out of or resulting from, (a) any breach of, or inaccuracy in, any representation or warranty made by Genzyme in this Agreement, or any breach or violation of any covenant or agreement of Genzyme in or pursuant to this Agreement, and (b) the gross negligence or willful misconduct by or of Genzyme, its Affiliates and their respective directors, officers, employees and agents. This indemnification excludes Losses arising out of Third Party Infringement Claims resulting from Genzyme's exercise in accordance with the terms of this Agreement of any intellectual property rights granted by Isis hereunder, including Genzyme's exercise of its rights under the Product-Specific Patents. Furthermore, Genzyme will have no obligation to indemnify the Isis Indemnitees to the extent that the Losses arise out of or result from, directly or indirectly, any breach of, or inaccuracy in, any representation or warranty made by Isis in this

Agreement, or any breach or violation of any covenant or agreement of Isis in or pursuant to this Agreement, or the negligence or willful misconduct by or of any of the Isis Indemnitees.

10.3.2. Indemnification by Isis. Isis will indemnify, hold harmless, and defend Genzyme, its Affiliates and their respective directors, officers, employees and agents ("Genzyme Indemnitees") from and against any and all Losses arising out of or resulting from, (a) any breach of, or inaccuracy in, any representation or warranty made by Isis in this Agreement, or any breach or violation of any covenant or agreement of Isis in or pursuant to this Agreement, (b) actions taken by Isis with respect to Mipomersen, the Product, the Licensed IP or the Product-Specific Patents prior to the Execution Date, and (c) the gross negligence or willful misconduct by Isis, its Affiliates, and their respective directors, officers, employees and agents. Isis will have no obligation to indemnify the Genzyme Indemnitees to the extent that the Losses arise out of or result from, directly or indirectly, any breach of, or inaccuracy in, any representation or warranty made by Genzyme in this Agreement, or any breach or violation of any covenant or

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

agreement of Genzyme in or pursuant to this Agreement, or the negligence or willful misconduct by or of any of the Genzyme Indemnitees.

10.3.3. Special Indemnification for Manufacturing Defects. Each Party will indemnify, hold harmless, and defend the other Party and its Affiliates and their respective directors, officers, employees and agents from and against any and all Losses arising out of or resulting from product liability claims resulting from the failure of any API or Product manufactured by such Party (or a Third Party on behalf of such Party) to conform to the applicable specifications or any failure of such Party (or a Third Party on behalf of such Party) to meet the standards of cGMP for the API or Product. Neither Party will have any obligation to indemnify the other Party and its related indemnitees to the extent that the Losses arise out of or result from, directly or indirectly, any breach of, or inaccuracy in, any representation or warranty made by the other Party in this Agreement, or any breach or violation of any covenant or agreement of the other Party in or pursuant to this Agreement, or the gross negligence or willful misconduct by or of any of the other Party or its related indemnitees. Notwithstanding the foregoing, the indemnification obligations of each Party set forth in this Section 10.3.3 (Special Indemnification for Manufacturing Defects) will only apply to the extent that there would be a Net Loss if such Damages were included in Program Costs in the applicable calendar year. In other words, the manufacturing Party will be required to indemnity the other Party under this Section 10.3.3 only to the extent there are insufficient Net Revenue in the applicable calendar year to permit such Damages to be fully credited as Program Costs.

10.3.4. Damages that are Program Costs. The indemnification obligations of each Party set forth in Section 10.3.1 (Indemnification by Genzyme) and 10.3.2 (Indemnification by Isis) will exclude any Losses resulting from Damages to the extent that the Indemnitee has been reimbursed for such Damages by virtue of the inclusion of such Damages in Program Costs.

10.3.5. Indemnification Procedure. In the event of any claim, suit, proceeding or action of a Third Party (a "Third Party Claim") giving rise to an indemnification obligation under this Section 10.3, the person or entity entitled to indemnification under this Section 10.3 (individually, an "Indemnitee"), will promptly notify the Party from whom indemnification is sought (the "Indemnifying Party"), in writing of the Third Party Claim (it being understood and agreed, however, that the failure by an Indemnitee to give notice of a Third Party Claim as provided in this Section 10.3 will not relieve the Indemnifying Party of its indemnification obligation under this Agreement, except and only to the extent that such Indemnifying Party is actually prejudiced as a result of such failure to give notice). The Indemnifying Party will manage and control, at its sole expense, the defense of the claim and its settlement. Within thirty (30) days after delivery of such notification, the Indemnifying Party may, upon written notice to the Indemnitee, assume control of the defense of such Third Party Claim with counsel reasonably satisfactory to the Indemnitee. The Indemnitee may participate therein

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

at its own expense; provided, however, that if the Indemnifying Party assumes control of such defense and the Indemnitee reasonably concludes, based on advise from counsel, that the Indemnifying Party and the Indemnitee have conflicting interests with respect to such Third Party Claim, the Indemnifying Party will be responsible for the reasonable fees and expenses of counsel to the Indemnitee solely in connection therewith; provided further, however, that in no event will the Indemnifying Party be responsible for the fees and expenses of more than one counsel in any one jurisdiction for all Indemnified Parties. If the Indemnifying Party does not assume control of the defense of the Third Party Claim within thirty (30) days after delivery of Indemnitee's notice of such claim and request for indemnification, the Indemnitee(s) may defend such Third Party Claim. Each Party will keep the other Party advised of the status of such Third Party Claim and the defense thereof, and the Indemnifying Party will consider recommendations made by the other Party with respect thereto. If the Indemnifying Party does assume control of the defense of the Third Party Claim, the Indemnifying Party will not agree to any settlement of such Third Party Claim or consent to any judgment in respect thereof that does not include a complete and unconditional release of the Indemnitee from all liability with respect thereto or that imposes any liability or obligation on the Indemnitee without the prior written consent of the Indemnitee. The Indemnifying Party will not be obligated to indemnify the Indemnitee(s) for any Third Party Claim settled by the Indemnitee(s) without the Indemnifying Party's prior written consent, which consent will not be unreasonably withheld, delayed or conditioned.

10.4. Insurance. The parties will obtain by the Execution Date and maintain at all times during the term of this Agreement, Products Liability Insurance, including Clinical Trial coverage, with reputable and financially secure insurance carriers each having an A.M. Best rating of [**] or better, to cover their respective indemnification obligations under Section 10.3 (Indemnification), with limits of not less than [**] dollars [**] per occurrence

and [**] dollars [**] in the aggregate. Each party will provide the other with a Certificate of Insurance evidencing this coverage within thirty (30) days after the Execution Date. Genzyme will have the right to maintain self-insurance with respect to all or a part of its insurance obligations under this Section 10.4.

Article 11.
TERM AND TERMINATION

11.1. Term. The term of this Agreement (the "Term") commences on the Effective Date and, unless earlier terminated in accordance with the provisions of this Article 11, will continue in perpetuity.

11.2. Termination.

11.2.1. Genzyme Right to Terminate. At any time during the Term, but following payment by Genzyme of the upfront license fee under Section 8.1, Genzyme will be entitled to terminate this Agreement by providing written notice to Isis of such

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

termination.

11.2.2. Termination for Material Breach.

(a) If either Party believes that the other Party is in material breach of this Agreement (other than with respect to Genzyme's failure to use Commercially Reasonable Efforts under Section 5.2.2 (Performance of the Development Program) or Section 6.1 (Commercialization Responsibilities) or Section 7.3 (Research Efforts), which is governed by Section 11.2.3 below), then the non-breaching Party may deliver notice of such breach to the other Party. In such notice, the non-breaching Party will identify the actions or conduct that it wishes such 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 other Party with respect to the actions that it may need to take to cure such breach. If the breach is curable, the allegedly 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 by providing written notice to the breaching Party.

(b) Notwithstanding the foregoing, if the allegedly breaching Party 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 (the "Other Party") of such dispute within such ninety (90) day period or such other reasonable cure period, as applicable, the Other Party will not have the right to terminate this Agreement in accordance with this Section 11.2.2 unless and until it has been determined in accordance with Article 13 (Dispute Resolution) that this Agreement was materially breached by the allegedly breaching Party and that Party fails to cure such breach within the allowed cure period following such determination. It is understood and acknowledge 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.

(c) This Section 11.2.2 will be subject to and will not limit the provisions of Section 11.2.3 (Termination by Isis for Failure of Genzyme to Use Commercially Reasonable Efforts) and Section 11.3 (Consequences of Termination).

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

11.2.3. Termination by Isis for Failure of Genzyme to Use Commercially Reasonable Efforts.

(a) Subject to Sections 11.2.3(b) and 11.2.3(c) below, Isis will have the right to terminate this Agreement on (i) a Major Market Country-by-Major Market Country basis if Genzyme is in material breach of its obligations to use Commercially Reasonable Efforts (A) under Section 5.2.2 (Performance of the Development Program) to develop the Product in such Major Market Country or (B) under Section 6.1 (Commercialization Responsibilities) to commercialize the Product in such Major Market Country and (ii) in its entirety if Genzyme is in material breach of its obligations to use Commercially Reasonable Efforts (A) under Section 5.2.2 (Performance of the Development Program) to develop the Product in all Major Market Countries or (B) under Section 6.1 (Commercialization Responsibilities) to commercialize the Product in all Major Market Countries or (C) under Section 7.3 (Research Efforts) to conduct research activities designed to advance a Product to the stage where it can be developed pursuant to a Development Plan. Notwithstanding the foregoing, the Agreement will not so terminate (in its entirety or in any particular Major Market Country) unless (x) Genzyme is given ninety (90) days prior written notice by Isis of Isis' intent to terminate, stating the reasons and justification for such termination and recommending steps which Genzyme should take and (y) Genzyme or its Sublicensee has not used good faith Commercially Reasonable Efforts in such Major Market Country(ies) during the ninety (90) day period following such notice to diligently pursue the development and/or commercialization of the Product.

(b) It is understood and acknowledged that if Genzyme (by itself or through its Affiliates or Sublicensees) uses Commercially Reasonable Efforts to research, develop or commercialize a Product in each and every Major Market Country, Genzyme will be deemed to be in compliance with its obligation under Section 5.2.2 (performance of Development Program), Section 6.1 (Commercialization Responsibilities) and Section 7.3 (Research Efforts) to use Commercially Reasonable Efforts to research, develop and commercialize a Product with respect to all countries in the world.

(c) If Genzyme disputes in good faith the existence or materiality of an alleged breach specified in a notice provided by Isis pursuant to Section 11.2.3(a) above, and provides notice to Isis of such dispute within the ninety (90) day period following such notice provided by Isis, Isis will not have the right to terminate this Agreement unless and until the existence of such material breach or failure by Genzyme has been determined in accordance with Article 13 and Genzyme fails to cure such breach within ninety (90) days 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.

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

(d) This Section 11.2.3 and Section 11.3 (Consequences of Termination) set forth Isis' sole and exclusive remedy for Genzyme's breach of its obligation to use Commercially Reasonable Efforts under Section 5.2.2 (Performance of the Development Program) or Section 6.1 (Commercialization Responsibilities) or Section 7.3 (Research Efforts).

11.3. Consequences of Termination. The following terms will apply on termination of this Agreement:

11.3.1. Licenses. Upon termination of this Agreement by either Party pursuant to this Article 11, the Product License will terminate and Genzyme, its Affiliates and Sublicensees will cease selling the Product.

11.3.2. Return of Information and Materials. Upon termination of this Agreement by either Party pursuant to this Article 11, 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. Notwithstanding the foregoing, the Parties will be permitted to retain one copy of such data, files, records, and other materials for archival purposes.

11.3.3. Accrued Rights. Termination of this Agreement 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. 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 clarification, (a) no milestone payments under Section 8.2 (Milestones) and (b) no payments under Section 8.5.2 (Sharing of Net Profits) will be payable by Genzyme following termination of this Agreement, except to the extent that the milestone event was achieved (in the case of milestone payments) or the Net Profits were achieved (in the case of net profit sharing) prior to such termination.

11.3.4. Survival. The following provisions of this Agreement will survive the expiration or termination of the Agreement: Section 6.5 (Safety Reporting), Section 8.8 (Audits and Interim Reviews), Section 9.3.2 (Terms of Sharing Agreement), Section 10.3 (Indemnification), Section 11.3 (Consequences of Termination), Section 11.4 (Remedies for Isis' Material Breach), Article 12 (Confidentiality), Article 13 (Dispute Resolution), and Article 14 (Miscellaneous).

11.3.5. Reversion.

(a) Isis Reversion Rights. If (a) Genzyme terminates the Agreement under Section 11.2.1 (Genzyme Right to Terminate) or (b) Isis terminates the Agreement under Section 11.2.2 (Termination for Material Breach) or Section 11.2.3 (Termination by Isis for Failure of Genzyme to Use Commercially Reasonable Efforts), Genzyme will:

(i) grant to Isis a non-exclusive, sublicensable, worldwide license to

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

any Product Trademarks, Genzyme Program Patents and other Patents owned or Controlled by Genzyme as of the date of termination that Cover the Product;

(ii) transfer to Isis, for Isis' use with respect to the development and commercialization of the Product, any data, results, Regulatory Materials and files in Genzyme's possession as of the date of termination that relate solely to the Product; and

(iii) re-assign to Isis the Product-Specific Patents assigned to Genzyme pursuant to Section 9.1.1 (Assignment of Product-Specific Patents) using a form of assignment substantially similar to the one attached as Exhibit E hereto (collectively with clauses (i) and (ii) above, the "Reversion").

(b) Limitation. Isis hereby agrees and acknowledges that it may only use the license granted and the materials transferred pursuant to clauses (a)(i) and (a)(ii) of Section 11.3.5(a) in connection with the development and commercialization of the Product for therapeutic

purposes.

(c) Consideration for Reversion Rights.

(i) In consideration for the rights granted and materials transferred by Genzyme to Isis under Section 11.3.5(a) above, Isis will pay to Genzyme a royalty on Net Revenue as follows: (a) [**] of Net Revenue if the Reversion occurs prior to [**], (b) [**] of Net Revenue if the Reversion occurs after the [**] but prior to the [**] and (c) [**] of Net Revenue if the Reversion occurs after the [**] and at the time of or after the [**].

(ii) Such payments will be governed by the financial provisions in Sections 8.6 (Periodic Reporting and Reconciliation), 8.7 (Audits and Interim Reviews), 8.9 (Withholding Taxes) and 8.10 (Interest on Late Payments). In addition, the definition of Net Sales will apply to Isis in the same way as they applied to Genzyme prior to such termination of the Agreement.

(iii) Notwithstanding the foregoing, in no event will the total royalty payable to Genzyme exceed the aggregate amount of Program Costs that Genzyme has contributed to the Product, with interest thereon at ten percent (10%) per calendar year, compounded monthly, net of any amounts paid for by Isis or covered by Net Revenue.

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

11.4. Remedies for Isis' Material Breach.

11.4.1. Termination of Committees and Information Sharing. If Isis materially breaches this Agreement and fails to cure such breach within the time periods provided under Section 11.2.2 (Termination for Material Breach) and Genzyme does not wish to terminate this Agreement in its entirety, then, in addition to any other remedies Genzyme may have under this Agreement or otherwise, Genzyme will have the right to do any or all of the following in Genzyme's discretion: (a) terminate Isis' right to participate in the JDC and JPC and any other subcommittees or working groups established pursuant to this Agreement, each of which will be disbanded; (b) terminate the participation of Isis in any ongoing research and development programs and Genzyme's funding obligations associated therewith, (c) make all decisions required to be made by such committees or the Parties collectively under this Agreement in connection with the development and commercialization of the Product, (d) exclude Isis from all discussions with Regulatory Authorities regarding Isis Products, (e) require Isis to assign to Genzyme all of Isis' right, title and interests in any IND or other Regulatory Materials then held by Isis pertaining to Products and any agreements with Third Parties related solely to the development or supply of the Product; (f) require Isis to enable Genzyme or a Third Party manufacturer to manufacture clinical and initial commercial quantities of the Product in lieu of Isis, with such transition occurring on a commercially reasonable timetable; (g) terminate Genzyme's obligation to make further disclosures of Know-How or other information to Isis pursuant to this Agreement (including pursuant to Section 5.4.2 (Transfer from Genzyme to Isis) and Section 6.4 (Isis Safety Database)), other than reports required by Section 8.6 (Periodic Reporting and Reconciliation) and as reasonably required to permit Isis to perform its remaining obligations under this Agreement. In addition, if Isis has not completed the development activities that are its responsibility under this Agreement, then Genzyme may, but will not be obligated to, assume all responsibility for all such development activities that would have otherwise been Isis' responsibility under the Agreement. Isis will cooperate with the foregoing and provide to Genzyme and its Third Party contractors all Know-How, assistance, assignments and other support reasonably requested to assist Genzyme in assuming complete responsibility for the development and manufacture of the Product in an efficient and orderly manner.

11.4.2. Genzyme's Right of Setoff. If Isis materially breaches this Agreement and fails to cure such breach within the time periods provided under Section 11.2.2 (Termination for Material Breach) and Genzyme does not wish to terminate this Agreement in its entirety, then, in addition to any other remedies Genzyme may have under this Agreement or otherwise (an "Isis Breach Event"), Genzyme may setoff against any amounts owed to Isis pursuant to Article 8 (Financial Provisions) its good faith estimate of the amount of any losses, damages and expenses incurred by Genzyme as a result of Isis' breach of this Agreement (the "Setoff Amount"). If Genzyme exercises its setoff right under this Section 11.4.2, Genzyme will provide Isis with a written certificate, signed by Genzyme's Chief Financial Officer, certifying that the amount setoff by Genzyme represents

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

Genzyme's good faith estimate of such losses, damages and expenses. Notwithstanding the foregoing, if Isis notifies Genzyme in writing that it disputes Genzyme's assertion that Isis is in material breach of this Agreement or the amount setoff by Genzyme, then (a) Genzyme will initiate the dispute resolution process set forth in Article 13 (Dispute Resolution), and (b) pending the Parties' agreement regarding the appropriate setoff (if any) or a determination by the mediator of the proper amount that Genzyme may setoff (if any) in accordance with Section 13.2 (Mediation), Genzyme will pay the Setoff Amount into an interest-bearing escrow account established for the purpose at a bank. If the Parties cannot settle their dispute by mutual agreement, then, in accordance with Section 13.2.2 (Mediation of Setoff Disputes) the mediator will determine (1) the amount (if any) that Genzyme may setoff against future payments to Isis going forward, and (2) whether any portion of the escrow account should be released to Isis. In the event that it is finally determined pursuant to Article 13 (Dispute Resolution) by a court of competent jurisdiction that Genzyme has setoff an amount that exceeds the amount of losses, damages and expenses actually incurred by Genzyme as a result of Isis' breach of this Agreement, then Genzyme will promptly pay Isis the amount of such excess, plus interest on such amount as provided for in Section 8.10 (Interest on Late Payments), with interest accruing from the time Genzyme applied such excess setoff.

Article 12.
CONFIDENTIALITY; PUBLIC DISCLOSURE

12.1. Non-Disclosure. Genzyme and Isis agree that all information relating to the Licensed IP, the terms and conditions of this Agreement, or any activities conducted in connection with or pursuant to this Agreement and disclosed by either Party in accordance with this Agreement ("Confidential Information") will be used and disclosed by the receiving Party only to perform its obligations and exercise its rights under this Agreement. Information relating to the development of the Product, the Licensed IP and the terms and conditions of this Agreement will be considered the Confidential Information of both Parties under the Agreement, as if both Parties were receiving Parties. Notwithstanding the foregoing, "Confidential Information" will not include information that the receiving Party can establish:

(a) was already known by the receiving Party (other than under an obligation of confidentiality) at the time of disclosure by the disclosing Party;

(b) was generally available to the public or otherwise part of the public domain at the time of its disclosure to the receiving Party;

(c) became generally available to the public or otherwise part of the public domain after its disclosure or development, as the case may be, other than through any act or omission of the receiving Party or any of its Affiliates;

(d) was disclosed to the receiving Party, other than under an obligation of

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

confidentiality, by a Third Party who had no obligation to the disclosing Party not to disclose such information to others; or

(e) was independently discovered or developed by or on behalf of the receiving Party without the use of any Confidential Information belonging to the disclosing Party.

12.2. Authorized Disclosure and Use. Notwithstanding the foregoing provisions of Section 12.1, each Party may disclose Confidential Information belonging to the other Party to the extent such disclosure is reasonably necessary to:

(a) prosecute or defend litigation,

(b) comply with applicable governmental laws and regulations (including the rules and regulations of the Securities and Exchange Commission); or

(c) make filings and submissions to, or correspond or communicate with, any government authority.

In the event a Party deems it reasonably necessary to disclose Confidential Information belonging to the other Party pursuant to clauses (a), (b) and (c) of this Section 12.2, the disclosing Party will to the extent possible give reasonable advance notice of such disclosure to the other Party and take reasonable measures to ensure confidential treatment of such information. Each Party will promptly notify the other Party upon becoming aware of any misappropriation or unauthorized disclosure or use of the other Party's Confidential Information.

12.3. Terms of Agreement. The Parties agree that the terms of this Agreement are confidential and will not be disclosed by either Party to any Third Party (except to a Party's professional advisors, including, without limitation, accountants, financial advisors, and attorneys) without prior written permission of the other Party; provided, however, that (a) either Party may make any filings of this Agreement required by Applicable Law in any country so long as such Party uses its reasonable efforts to obtain confidential treatment for portions of this Agreement as available, consults with the other Party, and permits the other Party to participate, to the greatest extent practicable, in seeking a protective order or other confidential treatment; (b) either Party may disclose this Agreement on a confidential basis to potential Third Party investors or acquirers or, in the case of Genzyme, to potential Sublicensees, in each case in connection with due diligence or similar investigations; and (c) a Party may publicly disclose, without regard to the preceding requirements of this Article 12 (Confidentiality), information that was previously publicly disclosed in compliance with such requirements.

12.4 Public Disclosures.

(a) The Parties have agreed upon, and from time to time will agree upon updates to, a communication strategy document containing detailed substantive messaging and a detailed fact sheet with respect to the development, regulatory

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

Approval process, manufacturing and commercialization of the Product (the "Communications Plan"). The Communication Plan will identify agreed spokespeople according to subject matter and will include a calendar detailing events (investor and medical meetings, earnings dates, etc) and anticipated new Product disclosures warranting press releases, updates to any slide presentation or other

communication materials. If the Parties are unable to agree upon the content of a particular disclosure in any update to the Communications Plan, then the Party to whom the Agreement assigns primary responsibility over the subject matter of the disclosure will have the right to decide upon the appropriate content. Accordingly, in the event of such a disagreement, Isis will have the right to decide upon the appropriate disclosure on scientific matters, and Genzyme will have the right to decide upon the appropriate disclosure for pre-clinical and clinical development, regulatory, and commercial matters. If any spokesperson identified in the Communications Plan leaves the employ of a Party or changes roles such that it is no longer appropriate for him or her to serve as a spokesperson, the Party who employs such spokesperson may designate a replacement.

(b) In addition, from time to time the JDC will approve a scientific and medical publication plan (the "Scientific Publication Plan"). The Parties will refrain from making any public communications or disclosures regarding the Product other than those set forth in the Communications Plan or as expressly contemplated by the Scientific Publication Plan. Without limiting the generality of the foregoing, except for the specific disclosures set forth in the Communication Plan or as otherwise expressly contemplated by the Scientific Publication Plan, each Party will refrain from making any public disclosures concerning (i) the status of any Approval, (ii) any application for any Approval, or (iii) any communication with or from any Regulatory Authority. Isis will refer to Genzyme, in its capacity as holder of the IND, NDA or other Approval (as applicable) for the Product, any questions it may receive concerning these matters that call for information beyond that provided in the Communications Plan.

(c) To the extent that either Party proposes to make any public disclosure that deviates from the Communications Plan, it will submit to the other Party an initial draft of any press release, slide presentation or other public communication for review and comment at least five (5) Business Days in advance of such proposed public communication. In such event, each Party will not make any public communication unless and until the Parties revise the Communications Plan in accordance with Section 12.4(a) so as to include the disclosure included in such proposed public communication. For public disclosures that do not deviate from the Communications Plan, each Party will submit to the other Party a draft of any such public communication for review and comment at least forty-eight (48) hours in advance of such public disclosure. Notwithstanding any other provision of this Agreement, however, each Party may at any time make any press release or other public communication as it determines, based upon the advice of counsel, to be necessary to comply with any public disclosure obligations under Applicable Laws (including securities laws), so long as the announcing Party

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

provides the other Party at least some advance notice (which will be at least forty-eight (48) hours whenever possible) regarding the proposed public disclosure. Genzyme may satisfy its notice obligation under this Section 12.4 by emailing *and* telephoning either Isis' Chief Executive Officer or Chief Operating Officer, and Isis may satisfy its notice obligation under this Section 12.4 by emailing *and* telephoning either the Genzyme Senior Vice President, Cardiovascular or the Genzyme Senior Vice President of Corporate Affairs.

(d) Each Party will promptly notify (and provide as much advance notice as possible to) the other of any event materially related to Products (including any regulatory Approval) so that the Parties may, subject to the provisions of subsections (a) and (b) of this Section 12.4, analyze the need to or desirability of publicly disclosing or reporting such event.

(e) In accordance with Section 2.7 (Third Party Agreements), Isis will promptly provide Genzyme with any draft publication relating to the Product submitted to it for review pursuant to any agreement with any Third Party and will exercise its rights under any such agreement to comment on such publication in consultation with and as reasonably requested by Genzyme. Isis will not enter into any agreement after the Execution Date that grants any Third Party the right to make public statements regarding the Product unless the form of such agreement is approved in advance by Genzyme.

(f) Unless otherwise contemplated by the Scientific Publication Plan, Genzyme will serve as the principal point of contact for any Third Party author intending to publish a scientific or medical publication on matters with respect to which Genzyme is assigned primary responsibility under this Agreement, and Isis will serve as the principal point of contact for any such author on matters with respect to which Isis is assigned primary responsibility under this Agreement.

Article 13.
DISPUTE RESOLUTION

13.1. Escalation. In the event of any dispute (other than a dispute regarding the construction, validity or enforcement of either Party's Patents, which disputes will be resolved pursuant to Section 13.3 (Jurisdiction; Venue; Service of Process)) arising between the Parties relating to, arising out of or in any way connected with this Agreement or any term or condition hereof, or the performance by either Party of its obligations hereunder, whether before or after termination of this Agreement that cannot be resolved by the Parties (each, a "Dispute"), either Party may make a written request that the Dispute be referred for resolution to the chief executive officers of each Party (or their designees) (the "Executives"). Within sixty (60) days of either Party's written request that the Dispute be referred to the Executives, the Executives will meet in person at a mutually acceptable time and location or by means of telephone or video conference to negotiate a settlement of a Dispute. Each Party may elect to have such Party's JDC representatives participate in such meeting, if desired, provided that it provides the other Party with reasonable

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

advance notice of such intent so as to enable the other Party to have its JDC representatives also participate in such meeting, if desired. If the Executives fail to resolve the Dispute within such sixty (60) day period and the Dispute concerns any matter that this Agreement delegates to the JDC for determination, then Genzyme will be entitled to resolve the Dispute in its sole discretion. For all other Disputes, in the event that the Executives fail to resolve the Dispute within such sixty (60) day period the Dispute will be referred to mediation under Section 13.2 (Mediation).

13.2. Mediation.

13.2.1. Mediation Generally. If a Dispute cannot be resolved pursuant to Section 13.1 (Escalation), the Parties agree to try in good faith to resolve any such Dispute by non-binding mediation administered by JAMS End Dispute in accordance with its commercial mediation rules. The mediation will be conducted by a single mediator appointed by agreement of the Parties who will have previous judicial experience, or failing such agreement by JAMS End Dispute in accordance with its commercial mediation rules. Unless otherwise mutually agreed upon by the Parties, the mediation proceedings will be conducted in Chicago. The Parties agree that they will share equally the cost of the mediation, including filing and hearing fees, and the cost of the mediator(s). Each Party will bear its own attorneys' fees and associated costs and expenses.

13.2.2. Mediation of Setoff Dispute.

(a) If Genzyme has exercised its setoff right under Section 11.4.2 (Genzyme's Right of Setoff) and there is a Dispute regarding whether Isis is in material breach of the Agreement or the proper amount of the setoff that the Parties are unable to resolve in mediation pursuant to Section 13.2.1 (Mediation Generally), then at the completion of such mediation the mediator will decide the following issues, which decision will be binding on the Parties pending final resolution of the Dispute by a court of competent jurisdiction:

(i) Whether the amount placed in escrow by Genzyme pursuant to Section 11.4.2 exceeds the mediator's objective good faith estimate of the amount of any losses, damages and expenses incurred or likely to be incurred by Genzyme as a result of Isis' breach of this Agreement;

(ii) What amount (if any) may Genzyme setoff against future payments to Isis under Section 11.4.2, which amount will represent the mediator's objective good faith estimate of the amount of any losses, damages and expenses incurred or likely to be incurred by Genzyme as a result of Isis' breach of this Agreement.

(b) If the mediator determines that the amount placed in escrow by Genzyme pursuant to Section 11.4.2 exceeds the mediator's objective good faith estimate of he amount of any losses, damages and expenses incurred or likely to be incurred

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

by Genzyme as a result of Isis' breach of this Agreement, the Parties will promptly cause the escrow agent to release to Isis the amount of such excess, plus interest accruing on such amount in the escrow account. The Parties will promptly cause the remaining amount in the account to be returned to Genzyme.

(c) If the mediator determines an appropriate amount that Genzyme may setoff against future payments to Isis under Section 11.4.2, Genzyme may setoff such amount directly, and will not be required to pay such amounts into any escrow account.

(d) The decisions rendered by mediator with respect to the distribution of funds from the escrow account and amount Genzyme may setoff going forward will be binding on the Parties pending resolution of the Dispute by the agreement of the Parties or by a court of competent jurisdiction in accordance with this Agreement.

13.2.3. Legal Remedies. If the Parties fail to reach an amicable agreement pursuant to the non-binding mediation process set forth in Section 13.2 (Mediation) within sixty (60) days of the matter being referred to Mediation, then either Party may pursue a legal remedy in accordance with Section 13.3 (Jurisdiction, Venue, Service of Process).

13.3. Jurisdiction; Venue; Service of Process.

13.3.1. Jurisdiction. Each Party by its execution hereof, (a) hereby irrevocably submits to the exclusive jurisdiction of the United States District Court located in Chicago, Illinois for the purpose of any Dispute arising between the Parties in connection with this Agreement (each, an "Action") and (b) hereby waives to the extent not prohibited by Applicable Law, and agrees not to assert, by way of motion, as a defense or otherwise, in any such Action, any claim that it is not subject personally to the jurisdiction of the above-named court, that its property is exempt or immune from attachment or execution, that any such Action brought in the above-named court should be dismissed on grounds of forum *non conveniens*, should be transferred or removed to any court other than the above-named court, or should be stayed by reason of the pendency of some other proceeding in any other court other than the above-named court, or that this Agreement or the subject matter hereof may not be enforced in or by such court and (c) hereby agrees not to commence any such Action other than before the above-named court. Notwithstanding the previous sentence a Party may commence any Action in a court other than the above-named court solely for the purpose of enforcing an order or judgment issued by the above-named court.

13.3.2. Venue. Each Party agrees that for any Action between the Parties arising in whole or in part under or in connection with this Agreement, such Party bring Actions only in the federal courts of the United States of America located in Chicago, Illinois and any appellate court having jurisdiction over appeals from

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

such courts. Each Party further waives any claim and will not assert that venue should properly lie in any other location within the selected jurisdiction.

13.3.3. Service of Process. Each Party hereby agrees that service of process made by registered or certified mail, return receipt requested, at its address specified pursuant to Section 14.5 (Notices), will constitute good and valid service of process in any such Action and (c) waives and agrees not to assert (by way of motion, as a defense, or otherwise) in any such Action any claim that service of process made in accordance with clause (a) or (b) does not constitute good and valid service of process.

Article 14.
MISCELLANEOUS

14.1. Change of Control of Isis.

14.1.1. Termination of Committees and Information Sharing. In the event of a Change of Control of Isis, Genzyme will have the right, exercisable by written notice to Isis or its successor in interest within ninety (90) days of the public announcement of the completion of such Change of Control, to do any or all of the following in Genzyme's discretion: (a) terminate Isis' right to participate in the JDC and JPC and any other subcommittees or working groups established pursuant to this Agreement, each of which will be disbanded; (b) terminate the participation of the successor to Isis in any ongoing research and development programs and Genzyme's funding obligations associated therewith, (c) make all decisions required to be made by such committees or the Parties collectively under this Agreement in connection with the development and commercialization of the Product, (d) exclude Isis or its successor from all discussions with Regulatory Authorities regarding Isis Products, (e) require Isis to assign to Genzyme all of Isis' right, title and interests in any IND or other Regulatory Materials then held by Isis pertaining to Products and any agreements with Third Parties related to the development or supply of the Product; (f) require Isis to enable Genzyme or a Third Party manufacturer to manufacture clinical and initial commercial quantities of the Product in lieu of Isis, with such transition occurring on a commercially reasonable timetable; (g) terminate Genzyme's obligation to make further disclosures of Know-How or other information to Isis pursuant to this Agreement (including pursuant to Section 5.4.2 (Transfer from Genzyme to Isis) and Section 6.4 (Isis Safety Database)), other than reports required by Section 8.6 (Periodic Reporting and Reconciliation) and as reasonably required to permit Isis to perform its remaining obligations under this Agreement. In addition, if Isis has not completed the development activities that are its responsibility under this Agreement, then Genzyme may, but will not be obligated to, assume all responsibility for all such development activities and setoff against amounts payable by Genzyme to Isis under this Agreement any expense incurred by Genzyme in connection with such development activities that would have been Isis' responsibility under the Agreement had the Change of Control not occurred.

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

Isis or its successor will cooperate with the foregoing and provide to Genzyme and its Third Party contractors all Know-How, assistance, assignments and other support reasonably requested to assist Genzyme in assuming complete responsibility for the development and manufacture of the Product in an efficient and orderly manner. For purposes of clarification, all Confidential Information of Genzyme in Isis' or its successor's possession following Genzyme's exercise of its rights under this Section 14.1 (Change of Control of Isis) will continue to be subject to all applicable provisions of this Agreement (including, without limitation, Article 12 (Confidentiality).

14.1.2. Purchase of Product Economics. In addition to the rights set forth in Section 14.1.1 (Termination of Committees and Information Sharing), in the event of a Change of Control of Isis, Genzyme will have the right to purchase all of Isis' rights to receive payments under the Agreement. If Genzyme elects to pursue this right, which election may be made by written notice to Isis or its successor of such election within one hundred and eighty (180) days of the public announcement of the completion of such Change of Control, the Parties will, for a period of sixty (60) days following notice of such election, negotiate in good faith a mutually acceptable fair market value. If the Parties cannot agree on a purchase price, Genzyme will have the option to have a Third Party determine the then-applicable fair market value of Isis' rights to receive payments under the Agreement (the "Valuation Price"). The Parties will select a mutually agreeable independent investment banking firm of national reputation to ascertain the Valuation Price. If the Parties are unable to agree on such identity of such investment banking firm within a sixty (60) day period, then each Party will select an independent investment banking firm of national reputation and the two designated firms will select a mutually agreeable third investment banking firm who will ascertain the Valuation Price. If Genzyme elects to purchase all of Isis' rights to receive payments under the Agreement at the price mutually agreed by the Parties or the Valuation Price, as applicable, such purchase will render the rights granted to Genzyme under this Agreement fully-paid and irrevocable, and the Parties will enter into a mutually satisfactory amendment to this Agreement effecting this simultaneously with the payment of such price. If Genzyme does not exercise the right to purchase all of Isis' rights to receive payments under the Agreement under this Section 14.1.2, the successor's economic rights under this Agreement will be unchanged.

14.2. Specific Performance. Each Party acknowledges and agrees that, in the event of any breach of this Agreement by such Party or any of its Affiliates, the non-breaching Party may be irreparably and immediately harmed and may not be able to be made whole by monetary damages. Without prejudice to any rights and remedies otherwise available, and notwithstanding Section 13.1 (Dispute Resolution Mechanism), the non-breaching Party will be entitled to seek equitable relief by way of injunction, specific performance or otherwise if the breaching Party or any of its Affiliates breaches any provision of this Agreement.

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

14.3. Governing Law. This Agreement will be governed by and interpreted in accordance with the laws of the State of New York without reference to its choice of laws or conflicts of laws provisions.

14.4. Waiver; Remedies Cumulative. The failure by either Party to take any action or assert any right hereunder will in no way be construed to be a waiver of such right, nor in any way be deemed to affect the validity of this Agreement or any part hereof, or the right of a Party to thereafter enforce each and every provision of this Agreement. Except as expressly provided in this Agreement, the rights and remedies provided for in this Agreement are cumulative and not exclusive, and the exercise of any right or remedy under this Agreement will in no way prejudice or be construed to be a waiver of any other right or remedy a Party may have under this Agreement or otherwise.

14.5. Notices. Any consent or notice required or permitted to be given or made under this Agreement by one of the Parties hereto to the other will be in writing and delivered by hand or sent by nationally recognized overnight delivery service, prepaid registered or certified air mail, or by facsimile confirmed by prepaid, registered or certified mail letter, and will be deemed to have been properly served to the addressee upon receipt of such written communication, in any event to the following addresses (or any updated address provided to the notifying Party in writing in accordance with this Section 14.5):

If to Genzyme:	Genzyme Corporation 500 Kendall Street Cambridge, Massachusetts 02142 Attn: General Manager, Cardiovascular Business Unit Fax: (617) 252-7553
with a copy to:	Genzyme Corporation 500 Kendall Street Cambridge, Massachusetts 02142 Attn: General Counsel Fax: (617) 252-7553
If to Isis:	Isis Pharmaceuticals, Inc. 1896 Rutherford Road Carlsbad, CA 92008 Attn: COO and CFO Fax: (760) 603-4650
with a copy to:	Isis Pharmaceuticals, Inc. 1896 Rutherford Road Carlsbad, CA 92008 Attn: General Counsel Fax: (760) 268-4922

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

14.6. Entire Agreement. This Agreement and all Exhibits and Schedules attached hereto (the terms of which are incorporated herein by reference) sets forth all the covenants, promises, agreements, warranties, representations, conditions and understandings between the Parties hereto with respect to the subject matter hereof and, as of the Execution Date, supersedes and terminates all prior agreements and understandings between the Parties (including the Prior Agreement and the Confidential Disclosure and Standstill Agreement dated as of September 19, 2007) and constitutes the entire agreement between the Parties with respect to the subject matter hereof. All Exhibits and Schedules referred to herein and other attachments hereto are intended to be, and hereby are, specifically incorporated herein and made a part of this Agreement. No subsequent alteration, amendment or modification to this Agreement will be binding upon the Parties unless in writing and duly executed by authorized representatives of both Parties.

14.7. Binding Effect; Assignment. This Agreement will inure to the benefit of and be binding upon the Parties and their respective successors and permitted assigns. Neither Party will assign this Agreement or any of its rights or obligations hereunder without the prior written consent of the other Party; provided, however, that (a) either Party may assign this Agreement or its rights or obligations hereunder to any of its Affiliates or to a purchaser or successor of substantially all the assets to which this Agreement relates, and (b) Isis may enter into one or more financial factoring arrangements with Genzyme's prior written consent, such consent not to be unreasonably withheld, delayed or conditioned.

14.8. Severability. If any term, covenant or condition of this Agreement or the application thereof to any Party or circumstance, to any extent, is invalid or unenforceable, then (a) the remainder of this Agreement, or the application of such term, covenant or condition to Parties or circumstances other than those as to which it is invalid or unenforceable, will not be affected thereby and each term, covenant or condition of this Agreement will be valid and be enforced to the fullest extent permitted by law; and (b) the Parties hereto covenant and agree to renegotiate any such term, covenant or application thereof in good faith in order to provide a reasonably acceptable alternative to the term, covenant or condition of this Agreement or the application thereof that is invalid or unenforceable, it being the intent of the Parties that the basic purposes of this Agreement are to be effectuated.

14.9. Further Assurances. 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 Agreement.

14.10. Independent Contractors. The status of the Parties under this Agreement will be that of independent contractors. No Party will have the right to enter into any agreements on behalf of the other Party, nor will it represent to any Third Party that it has any such right or authority. Nothing in this Agreement will be construed as establishing a partnership or joint venture relationship between the Parties hereto.

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

14.11. Interpretation. The article and section headings herein are for reference purposes only and will not affect the meaning or interpretation hereof. The term "including" (or any variation thereof such as "include") will be without limitation.

14.12. Counterparts. This Agreement may be executed in one or more counterpart copies, and by facsimile signature, each of which will be deemed an original and all of which taken together will be deemed to constitute one and the same instrument.

14.13. Rights in Bankruptcy. All rights and licenses now or hereafter granted under or pursuant to this Agreement, including Section 2.1 of this Agreement, are rights to "intellectual property" (as defined in Section 101(35A) of Title 11 of the United States Code, as amended (such Title 11, the "Bankruptcy Code")). Isis hereby grants to Genzyme and all Affiliates of Genzyme a right of access and to obtain possession of and to benefit from (a) copies of research data, (b) laboratory samples, (c) samples of Product, (d) formulas, (e) laboratory notes and notebooks, (f) data and results related to clinical trials, (g) regulatory filings and approvals, (h) rights of reference in respect of regulatory filings and approvals, (i) pre-clinical research data and results, (j) marketing, advertising and promotional materials, all of which constitute "embodiments" of intellectual property pursuant to Section 365(n) of the Bankruptcy Code and (k) all other embodiments of such intellectual property, in each case, solely in connection with Genzyme's rights under this Agreement, whether any of the foregoing are in Isis' possession or control or in the possession and control of Third Parties. Isis agrees not to interfere with Genzyme's and its Affiliates' exercise of rights and licenses to intellectual property licensed hereunder and embodiments thereof in accordance with this Agreement and agrees to use Commercially Reasonable Efforts to assist Genzyme and its Affiliates to obtain such intellectual property and embodiments thereof in the possession or control of Third Parties as reasonably necessary or desirable for Genzyme or its Affiliates to exercise such rights and licenses in accordance with this Agreement. The Parties hereto acknowledge and agree that all payments by Genzyme to Isis under this Agreement, other than the commercial milestones payable pursuant to Section 8.2.2 and the sharing of Net Profits pursuant to Section 8.5.2, do not constitute "royalties" within the meaning of Bankruptcy Code §365(n) or relate to licenses of intellectual property hereunder.

[remainder of page intentionally left blank]

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

IN WITNESS WHEREOF, the Parties have caused this License and Co-Development Agreement to be executed by their officers thereunto duly authorized as of the date first written above.

Genzyme Corporation

By: /s/ Henri A. Termeer
Name: Henri A. Termeer
Title: Chairman, President
and Chief Executive Officer

Isis Pharmaceuticals, Inc.

By: /s/ B. Lynne Parshall
Name: B. Lynne Parshall
Title: Chief Operating Officer and
Chief Financial Officer

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

SCHEDULE 1.35

ISIS METHODOLOGY FOR DETERMINING ITS COST OF MANUFACTURE

[**]

SCHEDULE 1.49

EXAMPLE CALCULATION OF INTERNAL DEVELOPMENT EXPENSES

[**]

SCHEDULE 1.52

ISIS CORE TECHNOLOGY PATENTS

[**]

SCHEDULE 1.56

ISIS MANUFACTURING & ANALYTICAL PATENTS

[**]

SCHEDULE 1.99

PRODUCT-SPECIFIC PATENTS

[**]

SCHEDULE 1.113

SPECIAL ISIS CORE TECHNOLOGY PATENTS

[**]

SCHEDULE 2.1

LICENSES TO THIRD PARTIES

[**]

SCHEDULE 10.2.2

THIRD PARTY AGREEMENTS

[**]

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

EXHIBIT A

DEVELOPMENT PLAN

[**]

EXHIBIT B

DEVELOPMENT BUDGET

[**]

EXHIBIT C

FORM OF SUPPLY AGREEMENT

MANUFACTURING AND SUPPLY AGREEMENT

This Manufacturing and Supply Agreement (the ***"Supply Agreement"***) is entered into as of the 24th day of June, 2008 (the "Effective Date") by and between **Isis Pharmaceuticals, Inc.** ("Isis") and **Genzyme Corporation** ("Genzyme"). Genzyme and Isis may each be referred to herein as a "Party" or together as

the "Parties". Capitalized terms not defined herein will have the meaning given to such terms in the License and Co-Development Agreement between the Parties dated June 24, 2008 (the ***"Agreement"***). The Parties agree as follows:

WHEREAS, the Parties have entered the Agreement to provide for the further development and commercialization of one or more Products, including Mipomersen;

WHEREAS, the Agreement provides that Isis will be responsible for the manufacture of the active pharmaceutical ingredient (API) of Mipomersen (***"API"***) for the phase II clinical trials, the Pivotal Trial(s) and the initial commercial launch of Mipomersen;

WHEREAS, the Parties agree that the terms of this Supply Agreement will apply to all manufactured lots of API made and supplied under the Agreement and this Supply Agreement.

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 hereto agree to this Supply Agreement as follows:

1. **Scope; Second Manufacturing Suite** – Isis will produce the bulk API for Mipomersen under cGMP conditions and in accordance with the Quality Agreement between the Parties and referencing this Supply Agreement (the "Quality Agreement"), in the amount specified in the applicable Firm Order for use for the phase II clinical trials, the Pivotal Trial(s) and the initial commercial launch of Mipomersen.

   Isis will use commercially reasonable efforts to have [**].

2. **Supply as of Effective Date.** As of the Effective Date, Isis has in its inventory the quantities of API, placebo, drug product and clinical trial material set forth on Exhibit B attached hereto (the ***"Existing Material"***).

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

---

3. **Supply through the end of 2008.** After the Execution date until the [**] in 2008, Isis will manufacture and supply the API consistent with the needs of the Development Plan, which are approximately [**] kilograms (the ***"2008 API"***).

4. **Supply after 2008; Forecasting Before NDA Filing.**

   (a) After January 1, 2009 until the NDA Filing under the Agreement, Isis and Genzyme will establish an 8 calendar quarter rolling forecast (the ***"Clinical Rolling Production Forecast"***) that sets forth a good faith estimate of the quantity of API for the Mipomersen Genzyme expects to receive from Isis within the following 8 calendar quarter period. This Clinical Rolling Production Forecast will be updated on the first business day of each subsequent calendar quarter by Genzyme. The first 4 calendar quarters of the Clinical Rolling Production Forecast constitute a firm order (each ***"Clinical Firm Order"***). Genzyme will provide one or more purchase orders for Clinical Firm Orders not previously submitted with each new Clinical Rolling Production Forecast. The fifth (5^{th}) calendar quarter of any Clinical Rolling Production Forecast shall be binding solely to the extent that Genzyme shall be required to order (and Isis shall only be required to supply) not more than [**]% and not less that [**]% of the API forecast therein once such calendar quarter becomes the first (1^{st}) calendar quarter for the Clinical Rolling Production Forecast. Quarters 6 through 8 are estimated quantities to be used for planning purposes only. Not later than 30 days after the Effective Date, Genzyme will provide Isis with the first Clinical Rolling Production Forecast, which will initially cover the 8 quarter period beginning January 1, 2009. The quantities set forth in a Clinical Firm Order will be binding on both parties, and Genzyme will be obligated to purchase from Isis, and Isis will be obligated to supply, the specified quantities of API.

   (b) Notwithstanding the foregoing, each Clinical Firm Order is subject to the following conditions:

   - Isis will not be required to supply during a calendar quarter more than an aggregate of [**] kilograms of API, unless agreed to in advance by Isis and further that the batch size is no larger than [**] kilograms unless agreed to in advance by Isis.

   - The minimum order size is [**] kilograms per calendar quarter unless agreed to in advance by Isis.

   (c) Isis agrees to use commercially reasonable efforts to supply Genzyme, upon request, with quantities in excess of the quantity restrictions described in this Section 4(b) above.

5. **Supply; Forecasting After NDA Filing.**

   (a) After the NDA Filing under the Agreement, Genzyme will establish an eight (8) calendar quarter rolling forecast (the ***"Commercial Rolling Production Forecast"***) that sets forth a good faith estimate of the quantity of API for the Mipomersen Genzyme expects to receive from Isis within the following eight (8) calendar quarter period. This Commercial Rolling Production Forecast will be updated not later than the first business day of each subsequent calendar quarter by Genzyme. The first [**] calendar quarters of the Commercial Rolling Production Forecast will constitute a firm order (***"Commercial Firm Order"***). Genzyme will provide one or more purchase orders for Commercial Firm Orders not previously submitted with each new Commercial Rolling Production Forecast. The [**] and [**] calendar quarters of any Commercial Rolling Production Forecast shall be binding solely to the extent that Genzyme shall be required to order (and Isis shall be required to supply) not more than [**]% and not less than [**]% of the API forecast therein once those calendar quarters become the first [**] quarters for the Commercial Rolling Production Forecast. Quarters [**] through [**] are estimated quantities to be used for planning purposes only. Not later than 30 days after the NDA Filing, Genzyme will provide Isis with the first Commercial Rolling Production Forecast. The quantities set forth in a Commercial Firm Order will be binding on both parties, and Genzyme will be obligated to purchase from Isis, and Isis will be obligated to supply, the specified quantities of API. Clinical Firm Orders and Commercial Firm Orders may each be referred to herein as ***"Firm Orders"***.

   (b) Notwithstanding the foregoing, each Commercial Firm Order is subject to the following conditions:

· Isis will not be required to supply during a calendar quarter more than an aggregate of 50 kilograms of API, unless agreed to in advance by Isis and further that the batch size is no

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

larger than [**] kilograms unless agreed to in advance by Isis. The minimum order size is [**] kilograms per order.

(c) Isis agrees to use commercially reasonable efforts to supply Genzyme, upon request, with quantities in excess of the quantity restrictions described in this Section 5(b) above.

6. Delivery

(a) Isis will deliver the Existing Material and the 2008 API as directed by the JDC.

(b) Each order submitted in satisfaction of a Firm Order obligation set forth in Section 4 or 5 above shall set forth Genzyme's proposed delivery date, which date shall not be less than 90 days after the submission of the order in question. Within 10 business days of receipt of an order from Genzyme, Isis will either (i) confirm Genzyme's proposed delivery date or (ii) enter into discussions with Genzyme about a mutually agreeable delivery date (each, a ***"Delivery Date"***). Isis will use commercially reasonable efforts to deliver the API ordered in each Firm Order by the applicable Delivery Date (but in any event Isis will deliver the API within thirty (30) days of the Delivery Date); *provided*, *however*, that Isis may deliver any quantities requested in a Firm Order thirty (30) days early. Isis will not be required to supply, nor will Genzyme be required to purchase, API in a quantity exceeding the Firm Order. The quantity of API specified in each Firm Order, invoiced and paid for will be the as-is gross mass of the API after lyophilization (i.e. including such amounts of water, impurities, salt, heavy metals, etc not exceeding limits permitted in the Specifications). In addition, so long as Isis supplies the quantity of API specified in the applicable Firm Order for Mipomersen within plus or minus [**]%, Isis will be deemed to have satisfied the amount specified in the Firm Order but Genzyme will nonetheless pay for the quantity of API specified in the Firm Order, whether it is less than or greater than the amount ordered.

7. Shortfall

(a) In the event that at any time Isis anticipates that it will be unable to supply at least [**]% (as permitted by Section 6 above) of the quantities of API set forth in an agreed-upon Firm Order in satisfaction of its obligation under Section 4 or 5 for any reason, including without limitation force majeure, Isis will notify Genzyme in writing as soon as possible upon the prediction or occurrence of such non-supply.

(b) If Isis cannot Manufacture as set forth in (a) above, upon written request by Genzyme Isis will transfer to Genzyme all documentation and information, and permit Genzyme to reference and use any regulatory filings, and otherwise fully cooperate with Genzyme to enable Genzyme to make or have made API for use by Genzyme in accordance with the Agreement.

8. Specifications; CofA

(a) For the API supplied by Isis under this Supply Agreement, Isis and Genzyme will mutually agree on the specifications for such API and will attach and/or reference such specifications in the applicable Firm Order (the ***"Specifications"***). If no Specifications are attached to or referenced in a Firm Order the Specifications for the Firm Order will be the same Specifications that applied to the previous Firm Order. The Specifications as of the effective date of this Supply Agreement are attached hereto as Exhibit A and will apply to 2008 API and the API that is part of the Existing Material.

(b) Prior to shipment of API, Isis shall provide Genzyme with a certificate from Isis' quality assurance department, or Isis' equivalent thereof, that includes the results of quality control tests that were performed on each batch of API manufactured in accordance with the Specifications and that indicates that the API contained in the shipment: (i) meets the Specifications and (ii) was manufactured in compliance with cGMPs and all other applicable laws and regulations (a ***"CofA"***).

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

9. API Pricing - The purchase price for API manufactured under this Agreement in 2008 is $[**] per kilogram, *except* the purchase price for Lot # CA301012-015 will be the [**] $[**] per kilogram and the purchase price set for API manufactured in 2009 under this Section. The purchase price for API manufactured in each subsequent calendar year in the Term shall be determined as follows: In September of each year, starting September of 2008, Isis will provide Genzyme a nonbinding, good faith estimate of the purchase price for API for the following year. By November 15 of each year, starting November 15, 2008, Isis will provide Genzyme the final purchase price (each, a ***"Purchase Price"***) applicable to the manufacture and supply of API scheduled for delivery in the following year. Such Purchase Prices will be binding on both Parties; *provided*, *however*, that such price will (i) not exceed $[**] per kilogram of API and (ii) represent Isis' good faith estimate of its fully-burdened cost to manufacture such API. This price includes all direct and indirect costs of manufacturing the API, including the cost of analytical work, raw materials, storing stability and retain samples, and, unless otherwise specifically stated in the applicable Firm Order, all other activities specified in the Specifications; *provided*, *however*, this price does not include stability testing, CMC work, process validation or other work to support regulatory filings. All payments are in US Dollars.

10. Terms of Payment –

(a) On the Execution Date, Isis will apply $[**] towards External Development Expenses under Section 8.3.1 of the Agreement for the Existing Material.

(b) For the 2008 API, Genzyme shall not be required to pay for the 2008 API, but rather upon transfer of such 2008 API Isis shall report the purchase price for the 2008 API as its Fully Absorbed Cost of Goods in reports submitted to Genzyme in accordance with Section 8.6 of the Agreement and such Fully Absorbed Cost of Goods shall be credited against Isis's obligations to fund the first one hundred and twenty-five million ($125 million) in External Development Expenses as contemplated by Section 8.3.1(b) of the Agreement.

(c) Until the earlier of (i) the first calendar quarter in which Net Revenue (as that term is defined in the Agreement) exceeds the aggregate Purchase Price for API in that calendar quarter and (ii) the date Isis has fully satisfied its obligation to fund the first one hundred and twenty-five million dollars ($125 million) of External Development Expenses in accordance with Section 8.3.1(b) of the Agreement, Genzyme shall not be required to pay the Purchase Price for Product ordered and transferred hereunder, but rather Isis shall report such Purchase Price as its Fully Absorbed Cost of Goods in reports submitted to Genzyme in accordance with Section 8.6 of the Agreement and such Fully Absorbed Cost of Goods shall be credited against Isis's obligations to fund the first one hundred and twenty-five million ($125 million) in External Development Expenses as contemplated by Section 8.3.1(b) of the Agreement.

(d) Once the condition described in either clause (i) or (ii) of Section 10(c) above has been satisfied, then the following payment terms shall apply to Product supplied hereunder:

- A pre-payment of 50% of the Purchase Price from Genzyme is payable in cash upon delivery of the applicable Firm Order.
- The remaining 50% of the Purchase Price is due in cash to Isis by wire transfer or other customary means within 30 days from the date of receipt of invoice, following title transfer from Isis to Genzyme or its designee of the API (in accordance with Section 12 below).
- In addition to the price stated in this Supply Agreement, Genzyme will pay to Isis all taxes and duties (except income tax) imposed upon Isis, in connection with the API and will reimburse Isis for the insurance and freight expenses discussed in Section 12 below.

11. Term – This Supply Agreement will remain in effect as long as Isis and Genzyme mutually agree for Isis to supply Mipomersen API as described in the Agreement.

12. Title & Transportation for Existing Material: Title to the Existing Material will transfer to Genzyme EXW (Incoterms 2000) Isis' facility following Isis' receipt of an Authorization to Ship letter from the

---

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

Genzyme's Quality Assurance Department authorizing shipment of the applicable Existing Material. Isis will insure against the replacement cost of the Existing Material until title transfers. The Parties will share the Risk of loss related to the Existing Material.

Isis will ship the Existing Material in accordance with the applicable Authorization to Ship letter from Genzyme's Quality Assurance Department. Isis will pay all freight for such transportation and include such costs as part of Isis' Fully Absorbed Cost of Goods.

13. Title & Transportation for other API: Title to the API supplied under Section 3, 4 or 5 above will transfer to Genzyme upon the earlier of (i) 15 days following the receipt by Genzyme of the CofA, a copy of the batch record and the QC release testing for the applicable order (unless Genzyme initiates formal dispute resolution regarding the API's failure to meet the warranty set forth in Section 17), (ii) EXW (Incoterms 2000) Isis' facility following Isis' receipt of an Authorization to Ship letter from the Genzyme's Quality Assurance Department authorizing shipment of the applicable API order, and (iii) the date pursuant to the dispute resolution it is determined that the API did meet the warranty set forth in Section 17. Isis will insure against the replacement cost of the API until title transfers. Risk of loss passes simultaneously with the title. Isis may deliver the applicable invoice to Genzyme for API contemporaneously with title transfer.

Isis will ship the API to Genzyme EXW (Incoterms 2000) upon the earlier of (i) the date such API is released by Isis' Quality Assurance Department and accepted by Genzyme's Quality Assurance Department via an Authorization to Ship letter, and (ii) 60 days following title transfer of such API. Transportation arrangements will be made by Isis as specified by Genzyme. Isis will pay all freight for such transportation and add such costs to the invoice as a separate line item.

14. Intellectual Property: The ownership and treatment of any intellectual property generated in the course of Isis' performance of this Supply Agreement will be governed by the Agreement.

15. CMC Work, Regulatory Support & Stability Testing –Genzyme will be responsible for all CMC work and regulatory filings associated with the API and drug product. Isis will not be responsible for CMC work, process validation or other work to support regulatory filings under this Supply Agreement. If Genzyme wishes to engage Isis to perform such work the Parties will mutually agree upon an appropriate plan and budget for executing such work.

Isis will manage the stability testing of any API manufactured under this Supply Agreement per Isis' current stability protocol (whether performed by Isis or an independent contractor). If performed by Isis, the price for the stability testing of the API will be $7,000 per time point per lot of API. If performed by a contractor, the price fro the stability testing of the API will be the price charged by the contractor. In either case, the price for the stability testing will be treated as Program Costs under the Agreement.

16. Hazards; Risk Sharing

If Isis encounters any difficulties or hazards during the manufacturing of a batch of API such that the delivery of API to Genzyme from that batch would constitute a breach of this Supply Agreement (including but not limited to the failure of such API to conform to the warranty set forth in Section 17), Isis will use commercially reasonable efforts to manufacture a replacement batch of API, such that Genzyme receives such API as close to the originally-scheduled delivery date as possible.

If the difficulty or hazard that causes the breach was not caused by Isis' gross negligence, the cost of the manufacture of the replacement batch will be shared by Genzyme and Isis as follows: Isis will be responsible for the [**] components for such batch of API; and, to the extent not reimbursable under Isis' insurance policies, Genzyme will be responsible for the [**] component and [**] expenses. In any year in which Net Profit is achieved under the Agreement, [**] components (and Genzyme's expenses for [**] and [**] expenses) for such replacement batch of API will be included as Program Costs under the Agreement with [**] included using the methodology referred to in the definition of Fully Absorbed Cost of Goods in the Agreement. For purposes of clarity and assuming none of the loss is covered

---

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

---

by Isis' insurance, the total price payable for such API will equal the price for such API originally specified above under Section 9 above or quoted in the Firm Order *plus* the [**] component and [**] expenses attributable to such replacement batch. However, if the difficulty or hazard that causes the breach was caused by Isis' gross negligence, the cost of the manufacture of the replacement batch will be solely Isis' responsibility and the price payable upon delivery of such API will equal the price for such API originally quoted in the Firm Order without any additional costs or expenses required to produce the replacement batch.

17. **Limited Warranty:** SUBJECT TO THE LIMITATIONS OF PARAGRAPHS, 18, 19 AND 21, Isis warrants, with respect to all the API, that, at the time of delivery, any API supplied by Isis will (a) meet the Specifications; (b) meet the standards of cGMP (for the API) and the requirements set forth in the Quality Agreement and (c) be conveyed with good title, free from any lawful security interest, lien or encumbrance.

18. **Disclaimer Of Warranties:** THE EXPRESS WARRANTIES CONTAINED IN PARAGRAPH 17 OF THIS SUPPLY AGREEMENT (AND THOSE MADE UNDER AND AS OF THE EFFECTIVE DATE OF THE AGREEMENT) ARE THE SOLE WARRANTIES WITH RESPECT TO THE API AND ARE MADE EXPRESSLY IN LIEU OF AND EXCLUDE ANY IMPLIED WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE AND ALL OTHER EXPRESS OR IMPLIED REPRESENTATIONS AND WARRANTIES PROVIDED BY COMMON LAW OR STATUTE.

19. **Limitation Of Remedies:** GENZYME'S EXCLUSIVE REMEDY AND ISIS' TOTAL LIABILITY TO GENZYME UNDER THIS SUPPLY AGREEMENT FOR CLAIMS BASED UPON SUPPLY OF THE API (OR FAILURE TO SUPPLY) (INCLUDING, WITHOUT LIMITATION, THOSE ARISING OUT OF STRICT LIABILITY, BREACH OF WARRANTY AND NEGLIGENCE) IS EXPRESSLY LIMITED TO THE REMEDY SET FORTH IN SECTIONS 7 AND 16 ABOVE.

    GENZYME WAIVES ALL OTHER CLAIMS BY GENZYME AGAINST ISIS UNDER THIS SUPPLY AGREEMENT WITH RESPECT TO SUPPLY OF THE API. NEITHER PARTY WILL BE UNDER ANY LIABILITY TO THE OTHER PARTY FOR ANY INCIDENTAL, CONSEQUENTIAL, SPECIAL, EXEMPLARY OR PUNITIVE DAMAGES ARISING FROM THIS SUPPLY AGREEMENT.

    THE LIMITATIONS IN THIS SECTION 19 DO NOT APPLY TO ANY CLAIM FOR INDEMNIFICATION UNDER SECTION 23.

20. **Quality Systems.** If Genzyme requests changes to Isis' quality systems or standard operating procedures, Isis and Genzyme will mutually agree on the scope and form of such changes and Genzyme will pay Isis to implement such changes at the then applicable Isis FTE Rate. Isis will be responsible to implement and pay for any modifications that either a Regulatory Authority requires or the Parties mutually agree are necessary to remain compliant with GMP or applicable ICH guidelines to manufacture API and Genzyme will pay for such modifications specific to the manufacturing of API that are not required by GMP or applicable ICH guidelines. The costs of implementation will include out of pocket costs as well as for the FTEs to implement such changes at the then applicable Isis FTE Rate.

21. **Inspection And Notice Of Claims:** Promptly upon receipt of each shipment of API, Genzyme will inspect and/or test (or cause to be inspected and tested if API is shipped to a third party) such API for any damage, defect or shortage. ALL CLAIMS (INCLUDING, WITHOUT LIMITATION, THOSE ARISING OUT OF STRICT LIABILITY, BREACH OF WARRANTY AND NEGLIGENCE) BY GENZYME WILL BE DEEMED WAIVED UNLESS MADE BY GENZYME IN WRITING AND RECEIVED BY ISIS WITHIN THIRTY (30) DAYS OF THE RECEIPT OF THE API.

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

---

22. **Force Majeure:** Neither Party will be liable for failures or delays in performance of any obligation under this Supply Agreement, other than for payment for API already transferred, to the extent that such failure or delay is caused by force majeure, being any event, occurrence or circumstance beyond the control of that Party (a "Force Majeure Event"), including but not limited to the following: failure or delay caused by or resulting from acts of God, strikes, earthquakes, fires, floods, accidents, wars, riots, acts of terrorism, restrictions imposed by any governmental authority (including allocations, priorities, requisitions quotas and price controls). The Party whose performance is affected by a Force Majeure Event will give prompt notice to the other Party stating the details and expected duration of the event.

23. **Indemnity.** Section 10.3 of the Agreement will apply to this Supply Agreement and the matters covered by this Supply Agreement.

24. Assignment: This Supply Agreement is not assignable or transferable by either Party without the prior written consent of the other Party; *provided that* a Party may assign the Supply Agreement to its successor in interest pursuant to the acquisition, merger or sale of all or substantially all of the assets of such Party, so long as such successor assumes in writing all of the assigning Party's obligations under this Supply Agreement.

25. Governing Law: The interpretation, validity, and performance of this document will be governed by New York law, without regard to any conflict-of-law rules.

26. Termination. Either Party will have the right to terminate this Supply Agreement if the other Party materially breaches its obligations under this Supply Agreement in accordance with Article 13 of the Agreement.

27. Survival: Sections 14 through 19, and 21 through 38 will survive expiration or termination of the Agreement. Any expiration or early termination of this Supply Agreement will be without prejudice to the rights of either Party against the other accrued or accruing under this Supply Agreement prior to termination. No expiration of this Supply Agreement will relieve a Party of its obligation to pay fees.

28. Inspections. Genzyme shall have the right to visit and inspect Isis' facility as further specified in the Quality Agreement. Isis's quality assurance department, or its equivalent, shall cooperate with Genzyme, as is reasonably necessary and useful at Genzyme's discretion, in any inspection conducted pursuant to this Section 28.

29. Notices: Any notice required or permitted to be given under this Supply Agreement by any Party will be in writing and will be (a) delivered personally, (b) sent by registered mail, return receipt requested, postage prepaid, (c) sent by a nationally-recognized courier service guaranteeing next-day or second day delivery, charges prepaid, or (d) delivered by facsimile (with the original promptly sent by any of the foregoing manners), to the addresses or facsimile numbers of the other Parties set forth below, or at such other addresses as may from time to time be furnished by similar notice by any Party. The effective date of any notice under this Supply Agreement will be the date of receipt by the receiving Party.

Notices will be sent to the following addresses or facsimile numbers:
In the case of Isis,

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008
Attention: VP, Manufacturing/Operations
Facsimile: 760-603-4655

With a copy to:
1. General Counsel (fax: 760.268.4922); and

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

2. Executive Vice President & CFO (fax: 760.603.4650)

In the Case of Genzyme:

Genzyme Corporation
200 Crossing Blvd.
Framingham, MA 01792
Attention: Senior VP, Materials Management
Facsimile: (508) 661-8538

With copy to:

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
Attn: General Counsel
Facsimile: (617) 252-7553

30. Waiver: No waiver of any term, provision or condition of this Supply Agreement whether by conduct or otherwise in any one or more instances will be deemed to be or construed as a further or continuing waiver of any such term, provision or condition or of any other term, provision or condition of this Supply Agreement.

31. Counterparts: This Supply Agreement and any amendment hereto may be executed in any number of counterparts, each of which will for all purposes be deemed an original and all of which will constitute the same instrument. This Supply Agreement will be effective upon full execution by facsimile or original, and a facsimile signature will be deemed to be and will be as effective as an original signature

32. Attachments: All attachments referred to herein form an integral part of this Supply Agreement and are incorporated into this Supply Agreement by such reference.

33. Inadvertent or Involuntary Omissions: The Parties acknowledge that they have expended substantial effort in preparing this Supply Agreement and attempting to describe in the Attachments, as thoroughly and precisely as possible, certain specifications and other information. However, despite these

efforts, the Parties acknowledge the possibility of involuntary or inadvertent omissions from the Attachments. The Parties will agree in writing to the changes to be made to the Attachments to add these inadvertent or involuntary omissions and any such written agreement executed by the Parties will serve as an amendment to this Supply Agreement.

34. Construction: Each Party to this Supply Agreement and its counsel have reviewed and revised this Supply Agreement. The rule of construction to the effect that any ambiguities are to be resolved against the drafting Party will not be employed in the interpretation of this Supply Agreement or any amendment or Attachment to this Supply Agreement. Capitalized terms used herein and not otherwise defined shall have the meaning ascribed to them in the Agreement.

35. Time: Time is of the essence in this Supply Agreement.

36. Preference: Unless otherwise specifically provided for in the Attachment, the terms of this Supply Agreement will prevail in the event of a conflict between this Supply Agreement and any such Attachments or the Quality Agreement.

37. Dispute Resolution: Article 13 of the Agreement will apply to any dispute under this Supply Agreement.

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

38. Entire Agreement: This Supply Agreement and the Quality Agreement constitute the full understanding of the Parties, and is the final, complete and exclusive statement of the terms and conditions of their agreement regarding the subject matter hereof. All representations, offers, and undertakings, of the Parties made prior to the signing of this Supply Agreement are hereby superseded. All amendments or modifications to this Supply Agreement must be in writing, identified as an Amendment to this Supply Agreement and signed by an authorized representative of each Party.

[remainder of this page intentionally left blank]

The Parties executing this Supply Agreement:

ISIS PHARMACEUTICALS, INC.	GENZYME CORPORATION
NAME: B. Lynne Parshall	NAME: Henri A. Termeer
TITLE: Chief Operating Officer and Chief Financial Officer	TITLE: Chairman, President and CEO
SIGNATURE: /s/ B. Lynne Parshall	SIGNATURE: /s/ Henri A. Termeer

[**]

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

EXHIBIT D

FORM OF QUALITY AGREEMENT

QUALITY AGREEMENT
Isis Pharmaceuticals and Genzyme Corporation.

The purpose of this Quality Agreement is to establish, clarify and communicate quality expectations for the manufacture and testing of API performed by Isis Pharmaceuticals, Inc., a Delaware corporation located in Carlsbad, California ("Isis") for Genzyme Corporation, a Massachusetts corporation with offices in Cambridge, Massachusetts ("Genzyme") for use in clinical trials or for launch supplies. For contractual responsibilities, refer to the Manufacturing and Supply Agreement dated June 24, 2008 (the "Supply Agreement").

WHEREAS, the Parties have signed the Supply Agreement contemporaneous with the present Quality Agreement;

WHEREAS, the Parties agree that the terms of this Quality Agreement will apply to all manufactured lots of active pharmaceutical ingredient (API) made and supplied under the Supply Agreement and this Quality Agreement. All changes to this Quality Agreement must be documented as an addendum to the original Quality Agreement, reviewed and approved by both parties' Quality Assurance representatives; and

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 hereto agree to this Agreement as follows:

1. Unless otherwise specified in this Agreement, the terms used in this Agreement shall have the meaning given to such terms in the Supply Agreement.

2. Isis will manufacture, produce and test the API in accordance with U.S. current Good Manufacturing Practices regulations (cGMP), ICH guidelines, and EMEA guidelines, and all such operations will be fully documented. Specific expectations are detailed in the Responsibility Checklist attached as Schedule 1. Genzyme will notify Isis if it is conducting a clinical trial that will require API to be manufactured in accordance with international guidelines that are more stringent than or different from cGMP or ICH Guidelines and the Parties will mutually agree on how to manufacture such API in accordance with such more stringent or different standards.

3. Isis will maintain adequately trained staff and appropriate records of training and competence. Isis will monitor and maintain records respecting its compliance with cGMP, including the process of establishment and implementation of the operating procedures and the training of staff as necessary to assure such compliance.

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

4. Isis will retain, in accordance with cGMP, full records (such as manufacturing batch records, analytical testing methods, analytical test results and appropriate reports) related to the API being manufactured and supplied.

5. Isis will provide approval/audit of the API using routine Quality Assurance (QA) procedures and will keep all appropriate records of such approval/audit processes conducted.

6. Isis will provide Genzyme with a copy of batch records, and a certificate of analysis (COA) which will contain (i) analytical results from Isis and any associated contract laboratories and (ii) a statement of compliance with cGMP, and signed by Isis QA. Isis will be responsible for the review, approval, and release of the API, and Genzyme retains full responsibility for the final release of the API for use in manufacturing Drug Product for use in clinical trials or commercially.

7. Isis will provide Genzyme with samples of the API including the appropriate documentation, if requested by Genzyme.

8. Original production and laboratory data and records will be retained and made available for review by Genzyme or its designees on-site at Isis.

9. Material changes to master batch records, specifications, test methods, and stability protocols (in each case as they apply to the API) will be agreed and approved by both parties.

10. Any raw material and component, which Isis will use for the production of API, will be tested and released utilizing Isis' cGMP compliant and approved specifications, sampling, testing and release procedures.

11. Isis will document and notify Genzyme of all significant changes to or deviations from the process or testing procedures and the investigations thereof. Documentation on process changes and deviations will be part of the batch record. A "Significant" change is understood as anything that deviates from the approved regulatory filing and/or anything reasonably likely to materially affect Safety, Identity, Strength, Purity or Quality (SISPQ). (This would not include changes such as use of a different but equivalent room, "like for like" equipment changes, etc.). In the event of an out of specification (OOS) result, Isis will promptly (within 2 business days) notify Genzyme on first confirmation of the OOS result.

12. Isis will ship or will arrange for third parties to ship all API to Genzyme or other designated site(s) in accordance with the Supply Agreement and with appropriate documentation and in suitable, labeled containers. This will also include the use of temperature monitoring devices if deemed by Genzyme necessary to ensure the quality of the API.

13. Isis will make available to Genzyme at Isis' facility, copies of all Isis Standard Operating Procedures used by Isis in connection with the manufacture of the API.

14. Isis will be responsible for qualification and routine compliance auditing of suppliers and subcontractors, in accordance with Isis' current procedures. Except for the subcontractors listed on Appendix B attached hereto, Isis will discuss with Genzyme in advance if Isis desires to use Subcontractors (Third Party) outside of Isis' approved list of subcontractors, and Genzyme will assess and approve, in advance, each subcontractor, such approval not to be unreasonably withheld.

15. Isis will inform Genzyme within 2 business days of a notice and result of any regulatory investigation by a Regulatory Authority (including any Genzyme documentation requested)

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

relating to any API or service being provided to Genzyme. Genzyme will have the opportunity to review and give input to the response to such investigations.

16. If Regulatory Authorities audit Genzyme, make investigations at Genzyme or ask questions of Genzyme about the activities conducted at Isis or third parties retained by Isis, then Isis will fully cooperate with Genzyme to provide adequate answers to and documentation for the Regulatory Authorities.

Isis will have the opportunity to review and give input to the response to such investigations.

17. Once every 12 months, a maximum of 3 Genzyme representatives will be entitled to visit and inspect ("audit") the production, manufacturing, quality control and warehousing facilities Isis is using in connection with the API, including the corresponding documentation. Such audit may not exceed three (3) business days, unless Genzyme representatives learn of a material deficiency that reasonably warrants an extension of the audit. Isis agrees to provide Genzyme with the necessary assistance and information. Genzyme will provide Isis with at least 4 weeks advanced notice of a requested inspection. As necessary, the Parties will mutually agree in good faith to additional inspections. In addition, with reasonable advance notice to Isis, Genzyme reserves the right to have a Genzyme representative present during manufacture of Genzyme product. Isis may limit Genzyme's presence at times when proprietary or confidential information of a Third Party unrelated to the Product could be observed.

18. Subject to applicable law, Isis will inform Genzyme within 2 business days, and *vice-versa*, on any matter which, in Isis' reasonable judgment, may have a bearing on drug safety or pharmaceutical quality in relation to the API, and supply all necessary information and cooperation for the investigation of such events. In cases where patient/subject safety may be concerned, Isis must inform Genzyme by telephone and in writing as soon as practicable, and *vice-versa*.

19. Isis will retain samples (initially at least 2X the amount needed to run all release testing) for all API produced.

20. Isis will maintain the API stability program in accordance with ICH guidelines and provide Genzyme with copies of all necessary documentation to establish API shelf-life. This includes the requirement to add at least one commercial API lot per year to the ongoing stability program as required under ICH guidelines.

21. In event of an out of specification (OOS) result encountered in release or stability testing, Isis QA shall promptly (within 2 business days of confirmation) notify Genzyme QA.

22. All product complaints, reported either from clinical studies, for example reported by principle investigator entities, clinical monitoring bodies or international authorities (e.g., customs) or product complaints related to commercial batches of Drug Product will be handled principally by Genzyme and supported by Isis in conjunction with Genzyme. All complaint events will be shared between both parties within 2 business days of receipt.

23. All primary data (or authenticated copies thereof) and result reports will be maintained in the Isis archives through a date specified in writing by Genzyme, which such date will not exceed 2 years after the final expiration date of the drug product in which the API was used. Thereafter, Genzyme will make arrangements for continued storage of such data at Genzyme's expense as is necessary.

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

24. The names of each responsible contact person(s) as of the Effective Date from Isis and Genzyme are listed in Appendix A.

The Parties Quality Assurance representatives executing this Agreement:

ISIS PHARMACEUTICALS, INC.	GENZYME CORPORATION
NAME: Jeff Jones	NAME: Charles Thyne
TITLE: Executive Vice President	TITLE: Vice President, Quality Operations
SIGNATURE: /s/ Jeff Jones	SIGNATURE: /s/ Charles Thyne
DATE: [illegible]	DATE: June 20, 2008

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

Appendix A

Key Contacts

Isis

Department	Primary Contact	Secondary Contact
Project Manager	[**], Development Chemistry & Manufacturing Telephone: [**]	[**], Development Operations Telephone: [**]
Analytical Development/Quality	[**], ADQC Telephone: [**]	[**], ADQC Telephone: [**]

Control		
Quality Assurance/Compliance	[**], QA/C Telephone: [**]	[**], QA/C Telephone: [**]
Regulatory Affairs	[**], RA Telephone: [**]	[**]. RA Telephone: [**]

Genzyme

Department	Primary Contact	Contact Information
Quality Assurance	[**] QA Director	
Quality Assurance	[**] Sr. Director CQC	[**]
Regulatory Affairs	[**] Associate Director Regulatory Affairs	[**]
Stability & Statistics	[**] Sr. Director Stability & Statistics	[**]
Project Management	[**] Sr. Project Manager	[**]

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

Appendix B

Pre-Approved Subcontractors

API Release

Test	Subcontractor
Bioburden	[**]
Endotoxin	[**]
Metals/Non-metals	[**]

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

Schedule 1. Responsibility Checklist

	Responsibility	Genzyme	Isis
1.0	**Regulatory Authorizations & cGMP Requirements**		
1.1	Maintains all licenses, registrations and other authorizations required to operate a cGMP pharmaceutical manufacturing facility under the Applicable Laws and will inform Genzyme of any changes covering these aspects within two (2) Business Days.		x
1.2	Maintains and operates its Facilities in compliance with cGMPs and other Applicable Laws.		x
1.3	Supplies all agreed upon information related to the manufacture of the API so that Genzyme QA can make the final determination on whether to use the API in Drug Product for clinical trials and commercial use.		x
1.4	Processes the API in accordance with cGMPs and other Applicable Laws.		x
1.5	Complies with the applicable TSE requirements (e.g. EMEA/410/01 in its current version) for starting materials, synthesis materials and reagents.		**x**
1.6	Operates the facility in a manner to prevent contamination and/or cross-contamination in conformance with cGMPs and other applicable regulations and guidelines (e.g., FDA Guidance for Industry Quality Systems Approach to Pharma cGMPs, Sept 2006).		x
1.7	Meets all Regulatory filing requirements for all API packaging configurations processed at its Facilities.		x
1.8	Performs annual Product Quality Review per applicable regulations	x	
1.9	Provides any API and (as applicable) Drug Product data needed to complete the annual Product Quality Review. Provides information to Genzyme in a timely manner, and in a format that facilitates review and inclusion in the Review prior to its due date.		x
1.10	Provides Isis with copies of those portions of the Marketing Applications, Marketing Authorizations and Clinical Trial Applications that are applicable to the API and drug product processing prior to submission and after review and approval from the applicable Regulatory Authority.	x	

1.11	Responsible for maintaining those portions of the Marketing Applications, Marketing Authorizations and Clinical Trial Application that are applicable to the Processing of the API at the Facilities for inspectional purposes.	x	
2.0	**Regulatory Actions & Inspections**		
2.1	Permits inspections by the Regulatory Authorities of all relevant premises, procedures and documentation.		x
2.2	Notifies the other party's QA within two (2) business days of the first Day of any FDA or other Regulatory Authority inspection or notice of inspection (or other business, for example sample collection) of the Facilities directly relating to the API.		x
2.3	Notifies the other party's Quality Assurance department within two (2) business days of any FDA or other Regulatory Authority investigation relating to the API.	x	x
2.4	Reviews any issued regulatory findings that directly relate to the API and reviews formal responses to the Regulatory Agency.	x	x
2.5	Reviews any issued regulatory findings that directly relate to the Isis facility and/or systems and approves formal responses to the Regulatory Agency.		x
2.6	Notifies the other Party within two (2) business days of any incident that causes the API or its labeling to be mistaken for, or applied to, another article or product and any information concerning any contamination or significant chemical, physical or other deterioration of shipped API.	x	x
2.7	Notifies the other party within two (2) business days of any Regulatory Authority request for API samples or API batch records prior to shipment.	x	x
2.8	Notifies the other party of any requests for information, notices of violation or other communication from a Regulatory Authority relating to environmental, occupational health and safety compliance relating directly to the API, within two (2) business days.	x	x

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

3.0	**Audits**		
3.1	Entitled to conduct one quality audit every 12 months to evaluate manufacturing, quality control and testing processes directly related to the API. Provides the other party with at least 4 weeks advanced notice of a requested inspection.	x	
		x	
	As necessary, the Parties will mutually agree in good faith to additional inspections.	x	
	Reserves the right to conduct additional audits in response to incidents/deviations associated with the manufacture/testing of the API.	x	
	Conducts each of the quality audits during normal business hours at mutually agreed upon times and by no more than three (3) audit tracks for three (3) days. Issues an audit report to the other party within 30 days of site audit.		x
	Completes responses to audit findings within 30 days of receiving audit report.		
3.2	Conducts internal audits of quality control and testing processes, in accordance with cGMPs and Applicable SOPs.		x
4.0	**Compliance of Specifications & Other Pertinent Controlled Documents & Change Control**		
4.1	Prior to the implementation of any changes which may directly impact product quality and prior to the submission of any such changes to the Regulatory Authorities, submits in writing those proposed changes to the intermediate and final product specifications, validated methods, and master manufacturing batch records to the other party for review and incorporation into their respective quality systems.		x
4.2	For any proposed changes related to the API and directly impacting product quality, approves in writing those changes to the intermediate and final product specifications, validated methods, master manufacturing batch records prior to the implementation of such changes and prior to the submission of any such changes to the Regulatory Authorities.	x	x
4.3	Notifies the other party prior to implementation of any proposed changes to the Facilities or to the processing equipment that directly impacts the API. Example: Introduction of new product sharing common equipment (e.g. freeze dryer).		x

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

4.4	Acts as a liaison with Regulatory Authorities for the approval, maintenance and updating of API Specifications and other pertinent information regarding applicable Marketing Authorizations.	x	

5.0	**Safety**		
5.1	Maintains safety/hazard and handling data on the Raw Materials, intermediates, and API.		x
5.2	Provides safety/hazard and handling data on the Raw Materials, intermediates, and API to Genzyme as requested.		x
6.0	**Complaints**		
6.1	Notifies the other party within two (2) business days of any product complaints associated with manufacturing of the API.	x	
6.2	Provides the other party with any information relating to the processing of the API that is necessary to address a product complaint and make any process changes necessary to address the complaint according to the Change Control procedures outlined in this document.		x
6.3	Collects and logs all information relating to product complaints.	x	
6.4	Investigates all product complaints.	x	x
6.5	Provides the other party with an investigation or interim report within 30 days of receiving notification of any product complaint associated with manufacturing of the API.		x
6.6	Issues all reports, customer responses and follow-up corrective actions relating to complaints and consults with the other party prior to any Recall or Product Withdrawal, provided Genzyme always maintains the final authority to make the decision.	x	
7.0	**Recall & Product Withdrawal**		
7.1	Notifies the other party within 2 business days of any events that could potentially result in a Recall or Product Withdrawal.		x
7.2	Notifies the other party of any Recall or Product Withdrawal which may be attributable to the manufacture of the API.	x	
7.3	Initiates and manages Recall or Product Withdrawal.	x	
7.4	Notifies appropriate Regulatory Authorities of Recall or Product Withdrawal.	x	
8.0	**Materials**		
8.1	Maintains Specifications for procurement of, storage of, sampling of, testing of and release of API Raw Materials and ensures such activities are conducted according to those Specifications.		x
8.2	Keeps retain samples of API Starting Materials for one (1) year beyond last expiration date of drug product manufactured using such API.		x

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

8.3	Keeps retain samples of API for three (3) years after either the completion of the last clinical trial or formal discontinuation of the last clinical trial in which the material was used.		x
8.4	Disposes of API waste and any regulated waste related to the processing of the API per local, state, and federal guidelines.		x
8.5	Executes a Vendor Qualification program for Raw Materials (including Starting Materials) that qualifies and confirms the Certificates of Analysis being relied upon.		x
8.6	Stores API and Raw Materials in accordance with approved Specifications while at their Facilities.		x
9.0	**Production & Validation**		
9.1	Maintains, qualifies and validates the Facilities, equipment and processes associated with Processing the API, including cleaning validation or verification.		x
9.2	Reviews and approves validation of processes directly associated with manufacturing of the API.	x	
9.3	Stores Validation Protocols and Reports, and upon request provides a copy of API related validation documentation to the other party. The other party must be informed before destruction of any Validation Protocols or Reports related to the API.		x
9.4	Manufactures and tests the API at the facilities in accordance with the Product Master Batch Records, the SOPs referenced therein and the Specifications.		x
9.5	Makes the final determination of whether to use the API in clinical trials or commercially.	x	
9.6	Uses appropriately validated or qualified analytical methods for routine API testing.		x
9.7	Maintains adequately trained staff and appropriate records of training and competence.		x
9.8	Generates Master Batch Record.		x
9.9	Approves Master Batch Record.	x	x
9.10	Generates Product Specifications.		x
9.11	Approves Product Specifications.	x	x
9.12	Supplies a Certificate of Analysis for the API to the other party reporting results versus the requirements of the Specifications.		x
9.13	Investigates, resolves and documents non-conformances and Deviations from the Master Batch Record directly relating to the API.		x

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

	Responsibility	Genzyme	Isis
9.14	Informs the other party in writing within 2 business days of occurrence of any Significant Deviation that may affect quality, safety, efficacy, or compliance with any license or Clinical Trial use of the API.		x

9.15	Notifies other party's QA, in writing of any API investigation and involves other party's QA in any corrective and preventive actions for Significant Deviations.		x
9.16	Provides copies of investigation reports to other party relating to all Significant Deviations related to the API.		x
9.17	Notifies other party's QA in writing before implementation of any planned Deviation: major, experimental, temporary or permanent, directly affecting any production of the API that may impact the IND, CTA, NDA or MAA.		x
9.18	Approves in writing any Planned Deviation: major, experimental, temporary or permanent, affecting any production of the API that may impact the IND, CTA, NDA or MAA.	x	x
9.19	Maintains all batch records for at least one (1) year after the expiry date. For APIs with retest dates, records should be retained for at least three (3) years after the batch is completely distributed.		x
9.20	Provides all documentation needed to maintain the Product Specification File in accordance with the applicable Regulatory Authorities for maintenance of the CTA, MAA.		x
9.21	Maintains the Product Specification File in accordance with applicable Regulatory Authorities.	x	
9.22	Labels API in accordance with internal procedures and regulatory requirements.		x
10.0	**Lot Number Assignment**		
10.1	Assigns lot numbers using internal procedures and communicates such lot numbers as soon as reasonable to facilitate tracking by the other party, as necessary.		x
11.0	**Samples**		
11.1	Samples API according to cGMPs and internal procedures.		x
11.2	Provides all non-USP reference standards required for testing API and drug product.		x
11.3	Samples for required applicable retain samples per Regulations and approved procedures.		x

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

11.4	Samples for required stability samples per approved procedures.		x
11.5	Stores all required retain samples per approved procedures while at Isis facilities.		x
11.6	As applicable, coordinates transfer of retain and/or stability samples for storage at other party's facilities.	x	
12.0	**Testing & Analysis**		
12.1	Performs API release and stability testing according to all approved agreements, specifications and party's applicable procedures.		x
12.2	Within two (2) business days, notifies the other party of any apparent OOS result, which cannot be invalidated by an assignable laboratory cause, generated during release or stability testing.		x
12.3	Provides a plan describing any proposed confirmatory or expanded testing of an apparent OOS result		x
12.4	Within two (2) business days of receiving a confirmatory or expanded testing plan, provides QA authorization to perform such testing.	x	x
12.5	Ensures that any confirmatory or expanded testing is performed according to an approved plan		x
12.6	Investigates all confirmed OOS results according to party's applicable procedures		x
12.7	Provides complete documentation of OOS investigation to other party, including final reported result(s), within two (2) business days of report completion.		x
13.0	**Stability Testing**		
13.1	Adheres to approved Stability Protocols.		x
13.2	Maintains Stability Program and provides documentation to support storage temperature and shelf-life for the duration of the Product life cycle.		x
13.3	Provides sample storage in temperature controlled stability chambers.		x
13.4	Provides stability data updates for time points as specified in the stability protocol.		x
13.5	Notifies the other party within 2 working days of confirmation of any initial stability failure of the API that has no assignable laboratory cause for the result.		x
13.6	Trends and analyzes all stability data.	x	x
13.7	Reviews stability reports related to the API.	x	x
14.0	**Release**		
14.1	Provides copies of documentation per section 15.0 pertaining to the manufacture of the API.		x
14.2	Authorizes shipment of API upon review and acceptance	x	

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

	of all required documentation and provides other party with written Authorization to Ship.		
14.3	Provides all necessary API release documentation to approved designated Third Party.		x
15.0	**Records Required for Release**		
15.1	Provides quality documentation for each batch of API. The list of required documents includes, but is not limited to: · Certificate of Analysis for API · Certificate of Conformance for API · Manufacturing Batch Record(s) for API · Analytical Forms / Records · Deviation/Investigation forms as part of the batch record		x

	· Signature of the QA representative who reviewed and approved the documentation and who is aware of any outstanding investigational issues with respect to the batch.		
15.2	Provides copies of all documentation necessary for the other party to respond to inquiries by Regulatory Authorities.		x
16.0	**Storage & Transportation**		
16.1	Stores the API at the Facilities according to the Specifications pending API release.		x
16.2	Will not ship the API to any other location without an Authorization to Ship from other party that may include specific conditions of insurance, packaging or courier service.		x
16.3	Transports under correct transport conditions to other or designated Third Party site.		x
17.0	**Training**		
17.1	Employees engaged in the manufacture, filling, storage and testing of Product shall have education, training and experience or any combination thereof, to enable that person to perform the assigned functions. · Training on the applicable procedures shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with requirements applicable to them. · All training will be documented in a training record for each employee. Employees will be trained with respect to data integrity and fraud.		x
18.0	**Quality Agreements**		
18.1	Review Quality Agreements every two (2) years and update as necessary.	x	x

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

EXHIBIT E

FORM OF PATENT ASSIGNMENT

PATENT ASSIGNMENT

WHEREAS, Isis Pharmaceuticals, Inc. (“Assignor”), a Delaware corporation with an address of 1896 Rutherford Road, Carlsbad, California 92008, is the owner of all rights, title, and interests in and to the patents and patent applications shown on the attached **Exhibit 1** (the “Patents”); and

WHEREAS, Genzyme Corporation (“Assignee”), a Massachusetts corporation with an address of 500 Kendall Street, Cambridge, Massachusetts 02142, desires to acquire the entire right, title, and interest in and to the Patents and all the inventions and discoveries disclosed in the Patents (the “Inventions”);

NOW THEREFORE, be it known that effective as of [ ], 2008, for good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, Assignor hereby sells, assigns, transfers, and sets over unto Assignee (1) the entire right, title, and interest in all countries throughout the world in and to said Patents and Inventions, including any renewals, revivals, reissues, reexaminations, extensions, continuations, continuations-in-part, and divisions of said Patents and any substitute applications therefor; (2) the entire right to file patent applications (“New Applications”) in the name of Assignee or its designee, or in the name of Assignor at Assignee’s or its designee’s election, on the aforesaid Inventions in all countries of the world; (3) the entire right, title, and interest in and to any patent which issued and may issue on the Inventions in any country, and any renewals, revivals, reissues, reexaminations, and extensions thereof, and any patents of confirmation, registration, and importation of the same; (4) the right to sue and recover for, and the right to profits or damages due or accrued in connection with, any and all past, present, or future infringements of the Patents and Inventions; and (5) the entire right, title, and interest in all convention and treaty rights of all kinds, including without limitation all rights of priority in any country of the world, in and to the above Patents and Inventions;

AND, Assignor hereby authorizes and requests the competent authorities to grant and to issue any and all patents on the Inventions throughout the world to Assignee, its successors, or assigns, whose rights, title, and interests in such patents are the same as would have been held and enjoyed by Assignor had this assignment, sale, and transfer not been made.

[Remainder of Page Left Blank]

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

IN WITNESS WHEREOF, the Assignor has caused this Patent Assignment to be duly executed by its officer thereunto duly authorized as of the [ ] day of [ ], 2008.

ISIS PHARMACEUTICALS, INC.

By: _____

Name:

Title:

STATE OF)
: ss.:
COUNTY OF)

On the day of , 200 , before me the undersigned, personally appeared , personally known to me or proved to me on the basis of satisfactory evidence to be the individual whose name is subscribed to the within instrument and acknowledged to me that he executed the same in his capacity, and that by his signature on the instrument, the individual, or the person upon behalf of which the individual acted, executed the instrument.

Notary Public

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

Acknowledgement of Assignee:

GENZYME CORPORATION

By:
Name:
Title:

STATE OF)
: ss.:
COUNTY OF)

On the day of , 200 , before me the undersigned, personally appeared , personally known to me or proved to me on the basis of satisfactory evidence to be the individual whose name is subscribed to the within instrument and acknowledged to me that he executed the same in his capacity, and that by his signature on the instrument, the individual, or the person upon behalf of which the individual acted, executed the instrument.

Notary Public

[**]

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

EXHIBIT F

DISCLOSURE SCHEDULE

[**]

[**] = Portions of this exhibit have been omitted pursuant to a confidential treatment request. An unredacted version of this exhibit has been filed separately with the Commission.

CONFIDENTIAL **EXECUTION VERSION**

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

PRODUCT DEVELOPMENT AND COMMERCIALIZATION AGREEMENT

BETWEEN

GLAXO GROUP LIMITED

AND

REGULUS THERAPEUTICS LLC

This **PRODUCT DEVELOPMENT AND COMMERCIALIZATION AGREEMENT** (this "**Agreement**") is entered into and made effective as of the 17th day of April, 2008 (the "**Effective Date**") by and between Regulus Therapeutics LLC, a Delaware limited liability company 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 limited liability company that was formed in 2007 by Isis Pharmaceuticals, Inc. ("**Isis**") and Alnylam Pharmaceuticals, Inc. ("**Alnylam**" and together with Isis, Regulus' "**Parent Companies**") as a joint venture pursuant to a Limited Liability Company Agreement dated September 6, 2007 between Alnylam and Isis (the "**Regulus LLC Agreement**"), the License and Collaboration Agreement dated September 6, 2007 entered into between Alnylam, Isis and Regulus (the "**Regulus License Agreement**") and the Services Agreement dated September 6, 2007 entered into between Alnylam, Isis and Regulus (the "**Services Agreement**" and together with the Regulus LLC Agreement and Regulus License Agreement, the "**JV Agreements**");

WHEREAS, Regulus possesses proprietary technology and know-how related to the research, discovery, identification, synthesis and development of single-stranded oligonucleotide miRNA Antagonists (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;

WHEREAS, GSK desires to engage in a collaborative effort with Regulus, wherein (i) Regulus will conduct [***] different Programs (as defined below) each directed against a particular Target (as defined below) to be identified in accordance with the procedures described herein, in order to discover, research and develop miRNA Antagonists, through to certain agreed-upon stages, and (ii) GSK shall have exclusive options, exercisable at GSK's sole discretion, at either the [***] (as defined below) or at [***] (as defined below), to further develop and commercialize Collaboration Compounds (as defined below) resulting from each of the [***] Programs on an exclusive basis for any and

---

all uses in the Field (as defined below) and in the Territory (as defined below), all on the terms and conditions set forth herein;

WHEREAS, upon GSK's exercise of any of its options to such Collaboration Compounds, Regulus desires to grant and will grant to GSK, and GSK desires to obtain and will obtain, an exclusive license in the Territory and in the Field under this Agreement to make, have made, use, sell, offer for sale, and import [***] Licensed Products (as defined herein) throughout the Territory, all on the terms and conditions set forth herein; and

WHEREAS, contemporaneously with the execution of this Agreement, the Parties have executed a separate Side Agreement with the Parent Companies ("**Side Agreement**") regarding certain matters pertaining to the relationship between the JV Agreements and this Agreement, and on or about the Effective Date, Regulus shall deliver to GSK a Convertible Promissory Note pursuant to which GSK shall lend Regulus the amount specified therein ("**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:

ARTICLE 1

DEFINITIONS

As used in this Agreement, the following terms shall have the meanings set forth in this Article 1 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.

1.1 "**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 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**").

1.2 "**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 Parent Companies of Regulus shall be deemed an Affiliate of Regulus for the purposes of this Agreement under any circumstances.

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

1.4 "**Agreement Term**" shall have the meaning assigned to such term in Section 12.1.4.

1.5 "**Alliance Manager**" shall have the meaning assigned to such term in Section 2.3.

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

1.7 "**ANDA**" shall mean 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).

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

1.9 "**Back-up Compound**" shall mean, with respect to a given Leading Compound for a given Program, any other Collaboration Compound Developed under such Program that is designed to inhibit (i.e. directed to or directed against) the same Collaboration Target as the Leading Compound and [***] the Leading Compound.

1.10 "**Bankruptcy Code**" shall have the meaning assigned to such term in Section 12.6.2.

1.11 "**Blocked Target**" shall mean a miRNA from [***] that Regulus elects, by written notice to GSK, [***] and that GSK does not, in accordance with [***].

1.12 "**Breaching Party**" shall have the meaning assigned to such term in Section 12.2.1 or Section 12.2.2, as the case may be.

1.13 "**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.

1.14 "**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.

1.15 "**Calendar Year**" shall mean a year of 365 days (or 366 days in a leap year) beginning on January 1st (or, with respect to 2008, the Effective Date) and ending December 31st, and so on year-by-year.

1.16 "**Candidate Selection Criteria**" shall mean the criteria for advancement of a Collaboration Compound [***], which provisional criteria are included in the Initial Research Plan with respect to Programs directed against the Initial Collaboration Targets (as such provisional criteria may be [***] in accordance with Section 2.1.6) and, with respect to Programs directed against the Subsequent Collaboration Targets, as confirmed by the JSC with respect to each such Program in accordance with Section 2.1.6. By way of guideline only, the Candidate Selection Criteria will typically include (a) data regarding the [***] of the Collaboration Compound and other [***] of the Collaboration Compound in [***] as well as a preliminary assessment of the [***], as well as evaluation of [***] models. An assessment of [***] should be typically included with preliminary [***], [***]; (b) the properties of the Collaboration Compound regarding [***]; (c) assessment of the [***]; and (d) a preliminary assessment of [***], (provided, however, that nothing herein shall require Regulus to resolve any such issues if they are identified).

1.17 "**[***]**" shall have the meaning assigned to such term in Section 4.1.1.

1.18 "**[***]**" shall have the meaning assigned to such term in Section 6.4.

1.19 "**[***]**" shall have the meaning assigned to such term in Section 4.2.1.

1.20 "**[***]**" shall have the meaning assigned to such term in Section 4.2.1.

1.21 "**[***]**" shall have the meaning assigned to such term in Section 4.2.1.

1.22 "**Candidate Selection Stage**" shall mean, as applicable, that stage of progression of a Research Program, or a Collaboration Compound within a Research Program, which is defined by the demonstration by Regulus (as confirmed by the JSC) that a Collaboration Compound within such Research Program has met the Candidate Selection Criteria and is ready for advancement into a [***]. For purposes of clarity, notwithstanding the foregoing, the Candidate

Selection Stage shall be deemed to have been achieved if, at any time during the Research Collaboration Term for a Research Program, GSK or the JSC requests that Regulus begin a [***] of a Collaboration Compound under such Research Program prior to Regulus' demonstration (and the JSC's confirmation) that a Collaboration Compound meets the Candidate Selection Criteria.

1.23 "**cGMP**" shall mean all applicable standards relating to manufacturing practices for fine chemicals, intermediates, bulk products or finished pharmaceutical products. For purposes of this Agreement, cGMPs shall mean the principles (a) detailed in the U.S. Current Good Manufacturing Practices, 21 CFR Parts 210, and The Rules Governing Medicinal Products in the European Community, Volume IV Good Manufacturing Practice for Medicinal Products, as each may be amended from time to time or (b) promulgated by any governmental body having jurisdiction over the manufacture of a Collaboration Compound, in the form of laws or regulations.

1.24 "**Chairperson**" shall have the meaning assigned to such term in Section 2.1.3.

1.25 "**Claims**" shall have the meaning assigned to such term in Section 11.1

1.26 "**Clinical Studies**" shall mean human studies designed to measure the safety, efficacy, tolerability and/or appropriate dosage of a Collaboration Compound or Licensed Product, 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).

1.27 "**Collaboration Compound**" shall mean any miRNA Compound [***] to [***] a Collaboration Target, which compound was either identified or discovered by Regulus or any of its Affiliates or any of its Parent Companies prior to the Effective Date or is discovered or identified by or on behalf of Regulus or any of its Affiliates during the Research Collaboration Term, and [***] of such miRNA Compound which is identified or discovered by or on behalf of Regulus or GSK pursuant to the Agreement.

1.28 "**Collaboration Know-How**" shall mean any Know-How pertaining to a Collaboration Compound or Licensed Product that is discovered, developed, invented or created solely by a Party and/or its Affiliates (or on behalf of such Party and/or its Affiliates by such Party's or its Affiliates' agents or contractors in accordance with Section 3.10), or jointly by or on behalf of the Parties and/or a Party's Affiliates (or on behalf of such Party and/or its Affiliates by such Party's or its Affiliates' agents or contractors in accordance with Section 3.10), in each case pursuant to activities conducted with respect to a Program during the relevant Program

Term in accordance with the Initial Research Plan, the relevant Research Plan or, if applicable, the relevant Early Development Plan.

1.29 "**Collaboration Patent**" shall mean any Patent Rights that claim or cover Collaboration Know-How.

1.30 "**Collaboration Target(s)**" shall have the meaning assigned to such term in Section 3.2.1 below.

1.31 "**Collaboration Technology**" shall mean the Collaboration Know-How and the Collaboration Patents.

1.32 "**Collaboration Term**" shall mean the period from the Effective Date until the end of the [***] with respect to all Programs hereunder.

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

1.34 "**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 a miRNA Therapeutic following receipt of Regulatory Approval for such miRNA Therapeutic.

1.35 "**Commercializing Party**" shall mean (a) GSK, with respect to any Collaboration Compounds other than Refused Candidates, and any Licensed Products other than Refused Candidate Products and Returned Licensed Products, in each case which are being Developed and Commercialized by or on behalf of GSK, its Affiliates or Sublicensees hereunder, and (b) Regulus, with respect to any Refused Candidates, Refused Candidate Products and/or Returned Licensed Products, in each case which are being Developed and Commercialized by or on behalf of Regulus, its Affiliates or Sublicensees hereunder.

1.36 "**Competitive Infringement**" shall have the meaning assigned to such term in Section 8.5.1.

1.37 "**[***]**" shall mean the [***] by Regulus of a [***] for such PoC Trial.

1.38 "**Confidential Information**" shall have the meaning assigned to such term in Section 9.1.

1.39 "**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 Parent Company of Regulus.

1.40 "**Convertible Promissory Note**" shall have the meaning assigned to such term in the Recitals.

1.41 "**CREATE Act**" shall have the meaning assigned to such term in Section 8.8.

1.42 "**[***]**" shall mean, with respect to any Collaboration Compound, a compound that is [***] from such Collaboration Compound or that is an [***] based thereupon, and that has, or is intended at the time of its synthesis to have, [***] the properties of the Collaboration Compound from which it was [***] and that is designed to [***] the same Collaboration Target as such Collaboration Compound.

1.43 "**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.

1.44 "**Development Candidate**" shall mean a Collaboration Compound that has been confirmed by the JSC to have satisfied the [***]. For purposes of clarity, (a) a Collaboration Compound shall be deemed a Development Candidate if, at any time during the Research Collaboration Term for a Research Program, GSK or the JSC by mutual agreement requests that Regulus begin [***] of such Collaboration Compound under such Research Program prior to confirmation by the JSC that such Collaboration Compound has met the [***] and (b) if Regulus has [***] a Collaboration Compound as a Development Candidate on or before [***] with respect to such Research Program, in which case, upon such expiration, Regulus shall provide a [***] with respect to the Leading Compound under such Research Program.

1.45 "**Diligent Efforts**" shall mean, with respect to the efforts to be expended by a Party with respect to any objective or obligation under this Agreement, such commercially reasonable, diligent and good faith efforts as such Party would normally use to accomplish a similar objective or perform a similar obligation under similar circumstances, acting reasonably promptly and in a sustained manner, and taking into account scientific, medical and commercially relevant factors such as (as applicable) stage of development, product life, patent position, strategic value, [***] market potential, medical, safety and regulatory issues, in accordance with the following:

1.45.1 *For Regulus*: Regulus shall apply its commercially reasonable Diligent Efforts in the conduct of all activities and obligations for which Regulus is responsible under this Agreement, in accordance with (a) the Initial Research Plan, (b) each Research Plan for each

Research Program, and (c) if GSK has not exercised its [***] with respect to a Program, the Early Development Plan for the relevant Early Development Program, in each case as established hereunder. Such efforts will be consistent at all times with the efforts and resources normally used by Regulus or, where one of its Parent Companies has already conducted or is actively conducting activities similar to those described in the Initial Research Plan, the relevant Research Plan or the relevant Early Development Plan, as applicable, but Regulus has not previously conducted such activities, the efforts and resources normally used by Regulus' Parent Company, in the exercise of Regulus' or its Parent Company's (as applicable) reasonable business discretion relating to the research and development progression of a compound in its own pipeline at a [***] as compared to the Collaboration Compound or Licensed Product in question.

1.45.2 *For GSK*: GSK shall apply commercially reasonable Diligent Efforts in the conduct of all activities and obligations for which GSK is responsible under this Agreement, including with respect to the further Development and Commercialization of a Leading Compound Developed under each Program for which GSK has exercised its Program Option hereunder. Such efforts will be consistent at all times with the manner and degree in which GSK in its reasonable business discretion would apply efforts and resources for a compound in its own pipeline, at a [***] as compared to the Collaboration Compound or Licensed Product in question.

1.45.3 A Party that is required to use Diligent Efforts with respect to an obligation shall, consistent with the standard described above: (a) promptly assign responsibility for such obligation to specific employee(s) or permitted contractors who are held accountable for progress and monitor such progress on an on-going basis, (b) establish and consistently seek to achieve specific, meaningful and measurable objectives for carrying out such obligation, and (c) consistently make and implement decisions and allocate reasonably sufficient personnel and financial resources designed to advance progress with respect to such objective.

1.46 "**Disclosing Party**" shall have the meaning assigned to such term in Section 9.1.

1.47 "**Discovery Milestone**" shall mean, on a Program-by-Program basis, the milestone event that is achieved hereunder upon the later of (i) demonstration of [***] confirmed by the JSC (subject to the dispute resolution provisions in Section 2.1.7, if necessary) or (ii) [***] for a given Program.

1.48 "**Early Development Plan**" shall mean an overall Development plan (including all subsequent amendments or updates thereto) for the Development of a Development Candidate through to Completion of the PoC Trial.

1.49 "**Early Development Program**" shall have the meaning set forth in Section 3.5.1.

1.50 "**Early Development Program Term**" shall define the duration of each Early Development Program hereunder and shall be determined on an Early Development Program-by-Early Development Program basis as follows: the period commencing upon the earlier of (a) the expiration of the [***] Exercise Period without GSK's exercise of the [***] for such Program, or (b) GSK's notice to Regulus of its decision not to exercise such [***], and ending upon [***]; provided, however, that such period shall terminate when GSK exercises the relevant [***] unless such Program is terminated earlier.

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

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

1.53 "**Enabling Studies**" shall have the meaning assigned to such term in Section 3.8.

1.54 "**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.

1.55 "**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).

1.56 "**Existing In-License Agreements**" shall have the meaning assigned to such term in Section 10.3.3.

1.57 "**Expert Panel**" shall have the meaning assigned to such term in Section 2.4.

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

1.59 "**Field**" shall mean (a) the [***] of any or all Indications and (b) also, to the extent that Regulus or GSK, whichever is the licensing Party hereunder, Controls [***] any or all Indications, to the extent such [***] are [***] to Commercialize a Licensed Product or where the absence of Control by the Commercializing Party, of [***] could reasonably be considered to materially adversely affect the sales of the Licensed Product.

1.60 "**Final Target Selection Date**" shall have the meaning assigned to such term in Section 3.2.1.

1.61 "**First Commercial Sale**" means, with respect to a Royalty-Bearing Product in a country in the Territory, the first sale, transfer or disposition for value to an end user of such Royalty-Bearing Product in such country; provided, that, the following shall not constitute a First Commercial Sale: (a) any sale to an Affiliate, Parent Company or Sublicensee unless the Affiliate, Parent Company or Sublicensee is the last entity in the distribution chain of the Royalty-Bearing Product, (b) any use of such Royalty-Bearing Product in Clinical Studies, pre-clinical studies or other research or development activities, or disposal or transfer of Products 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.

1.62 "**Former Target**" shall have the meaning assigned to such term in Section 3.2.1.

1.63 "**FTC**" shall have the meaning assigned to such term in Section 4.2.6.

1.64 "**Fully Absorbed Costs of Goods**" shall mean, with respect to the Manufacture of units or components of Collaboration Compounds or Licensed Products (including bulk drug substance), the fully-absorbed actual cost of supplying the Collaboration Compounds or Licensed Products to Regulus, GSK or a designee of either such Party as calculated under US GAAP or IFRS, as applicable, and consistent with such Party's or, with respect to Regulus, the applicable Parent Company's, methodology for other products. Specifically this shall include:

(a) if Manufactured by Regulus (or its Parent Company) or GSK, the Fully Absorbed Manufacturing Cost ("FAMC") as described in Schedule 1.64, including without limitation incremental and/or reasonably allocable overhead costs incurred including: [***] provided, however, that with respect to Manufacture by Regulus or one of its Parent Companies and if [***], the Parties shall agree in good faith to the costs with respect to the Manufacture of Collaboration Compounds or Licensed Products, based, at least in part, on such definition; or

(b) if Manufactured by a Third Party contract manufacturer, the actual costs of procuring such Collaboration Compounds or Licensed Products from such Third Party contract manufacturer, including any [***] payable to such Third Party contract manufacturer.

1.65 "**Fundamental IP**" shall have the meaning assigned to such term in Section 6.8.1.

1.66 "**Generic Product**" shall mean a Third Party's product(s) or Third Parties' product(s) having the same or substantially the same active pharmaceutical ingredient as a Royalty-Bearing Product and for which in the US an ANDA has been filed naming the Royalty-Bearing Product as the reference listed drug or ex-US, an equivalent process where bioequivalence to the Royalty-Bearing Product has been asserted.

1.67 "**GLP**" shall mean 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.

1.68 "**[***]**" shall mean a [***] study that is conducted in [***] that is conducted in compliance with GLP and is required to meet the requirements for filing an IND.

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

1.70 "**GSK Collaboration Know-How**" shall have the meaning assigned to such term in Section 8.1.2.

1.71 "**GSK Collaboration Patents**" shall have the meaning assigned to such term in Section 8.1.2.

1.72 "**GSK Collaboration Technology**" shall have the meaning assigned to such term in Section 8.1.2.

1.73 "**GSK Diligence Failure Event**" shall have the meaning assigned to such term in Section 12.2.4.

1.74 "**GSK Enabling Studies Know-How**" shall mean any Know-How conceived or reduced to practice by or on behalf of GSK or its Affiliates during the course of conducting Enabling Studies.

1.75 "**GSK Enabling Studies Patents**" shall mean all Patent Rights which claim or cover GSK Enabling Studies Know-How.

1.76 "**GSK Know-How**" shall mean any Know-How to the extent pertaining specifically and primarily to a Collaboration Compound or Licensed Product that (a) is Controlled by GSK and/or its Affiliates on the Effective Date or during the Agreement Term; and (b) is [***] for Regulus (i) to conduct activities for which Regulus is responsible under the Initial Research Plan, Research Plan and/or Early Development Plan during the Collaboration Term; or (ii) to Develop, Manufacture or Commercialize Refused Candidates, Refused Candidate Products and Returned Licensed Products. GSK Know-How shall exclude Collaboration Know-How, but shall include GSK Enabling Studies Know-How.

1.77 "**GSK Patents**" shall mean all Patent Rights in the Territory Controlled by GSK and/or its Affiliates as of the Effective Date or during the Agreement Term, to the extent containing a claim which [***] to a Collaboration Compound and which is [***] for Regulus (a) to conduct activities for which Regulus is responsible under the Initial Research Plan, Research Plan and/or Early Development Plan during the Collaboration Term; or (b) to Develop,

Manufacture or Commercialize Refused Candidates, Refused Candidate Products and Returned Licensed Products. GSK Patents shall exclude Collaboration Patents, but shall include GSK Enabling Studies Patents.

1.78 "**GSK Patent Royalty**" shall have the meaning assigned to such term in Section 6.6.1.

1.79 "**GSK Technology**" shall mean any GSK Patents and GSK Know-How, excluding any Collaboration Technology owned by GSK either jointly or solely.

1.80 "**HSR**" shall have the meaning assigned to such term in Section 4.2.6.

1.81 "**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).

1.82 "**Indemnitee**" shall have the meaning assigned to such term in Section 11.3.

1.83 "**Indication**" shall mean any [***] (to the extent that Regulus or GSK, whichever is the licensing Party hereunder, Controls [***]) [***], or [***], or [***].

1.84 "**Initial Collaboration Target**" shall have the meaning assigned to such term in Section 3.2.1.

1.85 "**Initial Research Plan**" shall mean the preliminary research plan attached hereto as Exhibit A, which plan sets forth (a) the activities of the Parties commencing on the Effective Date until the Final Target Selection Date, including the Collaboration Target selection process, Screening Assays to be conducted, and contemplated time periods associated with such activities, and (b) a general description of the types of activities to be conducted by the Parties during the remainder of the Collaboration Term. For purposes of clarity, upon final JSC approval of the Research Plan with respect to any Program, the terms of such Research Plan shall supersede the terms of the Initial Research Plan with respect to such Program.

1.86 "**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.

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

1.88 "**Joint Patent Subcommittee**" shall have the meaning assigned to such term in Section 2.2.2.

1.89 "**Joint Program Subcommittee**" or "**JPS**" shall have the meaning assigned to such term in Section 2.2.1.

1.90 "**Joint Steering Committee**" or "**JSC**" shall have the meaning assigned to such term in Section 2.1.

1.91 "**Jointly-Owned Collaboration Know-How**" shall have the meaning assigned to such term in Section 8.1.2.

1.92 "**Jointly-Owned Collaboration Patents**" shall have the meaning assigned to such term in Section 8.1.2.

1.93 "**Jointly-Owned Collaboration Technology**" shall have the meaning assigned to such term in Section 8.1.2.

1.94 "**JV Agreements**" shall have the meaning assigned to such term in the Recitals.

1.95 "**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.

1.96 "**Leading Compound**" shall mean the furthest advanced Collaboration Compound under a given Program.

1.97 "**Licensed Product(s)**" shall mean any miRNA Therapeutic having one or more Collaboration Compounds as an active ingredient(s). For purposes of clarity, Licensed Products include Combination Products.

1.98 "**Losses**" shall have the meaning assigned to such term in Section 11.1.

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

1.100 "**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.

1.101 "**Manufacturing Patents**" shall have the meaning assigned to such term in Section 6.6.2.

1.102 "**Milestone Event**" shall have the meaning assigned to such term in Section 6.4.

1.103 "**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 [***]. The miRNAs exemplified in miRBase (http://microrna.sanger.ac.uk/) as of the Effective Date are specified in Schedule 1.103, however, the Parties understand that the content of such database may change after the Effective Date.

1.104 "**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 [***].

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

1.106 "**miRNA Library**" shall mean a library of oligonucleotides [***] modulate the activity of miRNAs [***], from which library Regulus shall identify the miRNA Pool through the conduct of Screening Assays in accordance with the Initial Research Plan. The library of oligonucleotides [***] however, the Parties understand that the content of such [***] may change after the Effective Date.

1.107 "**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.

1.108 "**miRNA Pool**" shall mean a prioritized list of [***] miRNAs to be identified in accordance with the procedures set forth in the Initial Research Plan and from which list GSK shall select up to [***] Collaboration Targets in accordance with the terms hereof, which list shall exclude (a) any Collaboration Target once selected by GSK, including any Former Targets,

Initial Collaboration Targets and Subsequent Collaboration Targets, and (b) any Blocked Targets.

1.109 "**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.

1.110 "**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.

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

1.112 "**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).

1.113 "**Net Sales**" shall mean, with respect to any Royalty-Bearing Product, the gross invoiced sales of such Royalty-Bearing Product sold by either (i) GSK, its Affiliates or Sublicensees or (ii), as the case requires, Regulus, its Affiliates or Sublicensees (in each case, the "**Selling Party**"), in finished product form, packaged and labelled 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 Royalty-Bearing Product; (c) [***] charges relating to such Royalty-Bearing Product, including [***] thereto; (d) [***] directly linked to the sales of such Royalty-Bearing 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 Parent Companies or direct Sublicensees.

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

In the event a Royalty-Bearing Product is sold as part of a Combination Product (as defined below), the Net Sales from the Royalty-Bearing 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 [***] price (determined substantially in accordance with the above) of the Royalty-Bearing Product 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 Royalty-Bearing 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 [***] 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 a Royalty-Bearing Product and other therapeutically active pharmaceutical compound(s).

1.114 "**Non-breaching Party**" shall have the meaning assigned to such term in Section 12.2.1 or Section 12.2.2, as the case may be.

1.115 "**Option Compound**" shall mean (a) a Collaboration Compound which has qualified as a Development Candidate under a Program, with respect to which Program GSK has notified Regulus that it plans to exercise its [***] Option, (b) if GSK has not exercised its [***] Option for a Program, a Collaboration Compound for which Regulus has Completed a PoC Trial conducted with such Collaboration Compound under such Program, with respect to which Program GSK has notified Regulus that it plans to exercise its [***], and (c) all other Collaboration Compounds Developed under, or that is otherwise [***] to interfere with or inhibit (i.e. is directed to or directed against) the Collaboration Target that is the subject of, the same Program as the Collaboration Compound set forth in the foregoing clauses (a) or (b), including any Back-up Compounds and Derivatives of any of the foregoing. For purposes of clarity, "Option Compounds" shall include all Collaboration Compounds Developed under a Program

with respect to which GSK has exercised a Program Option or where pursuant to the termination of a Program, GSK acquired exclusive rights to the Collaboration Compounds of such Program in accordance with Article 12, regardless of whether or not any such Collaboration Compound has qualified as a Development Candidate or has satisfied the PoC Criteria.

1.116 "**Option Period**" shall mean any option exercise period applicable with respect to a Program Option hereunder.

1.117 "**Option Period Extension**" shall have the meaning assigned to such term in Section 4.2.6.

1.118 "**Parent Company**" shall have the meaning assigned to such term in the Recitals.

1.119 "**Parent Company Know-How**" shall mean, with respect to each Parent Company, all Know-How Controlled by such Parent Company on the Effective Date or during the term of the Regulus License Agreement (except as otherwise expressly provided therein) that relates to:

(a) miRNA Compounds or miRNA Therapeutics in general,

(b) specific miRNA Compounds or miRNA Therapeutics,

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

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

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

provided, however, that in each case (i) for any such Know-How 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 Know-How 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 Know-How will be included as Parent Company Know-How and (ii) Parent Company Know-How does not include [***]).[***]

1.120 "**Parent Company Patents**" shall mean, with respect to each Parent Company,

(a) all Patent Rights Controlled by such Parent Company on the Effective Date and listed on Exhibit B hereto, and

(b) all Patent Rights Controlled by such Parent Company during the term of the Regulus License Agreement (except as otherwise expressly provided therein) 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 Parent Company Patents, and (y) Parent Company Patents do not include [***]).

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

1.122 "**Patent Costs**" shall mean the reasonable fees and expenses paid to [***] and [***] and other reasonable [***]expenses paid to[***] incurred in connection with the Prosecution and Maintenance of Patent Rights.

1.123 "**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.

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

1.125 "**Payor**" shall mean the Commercializing Party and, with respect to milestone payments, GSK.

1.126 "**Pending Claim**" shall have the meaning assigned to such term in Section 6.6.2.

1.127 "**Permitted Licenses**" shall mean a license granted by a Parent Company to a Third Party to enable such Third Party to [***] but not to engage in any [***], where such Third Party is primarily engaged in [***] and is not engaged in any [***] activities with respect to any

Collaboration Targets. As used in this definition, the term "drug" includes, in addition to [***] and other [***].

1.128 "**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.

1.129 "**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.

1.130 "**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.

1.131 "**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.

1.132 "**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.

1.133 "**PoC**" shall mean the confirmation by the JSC or by GSK in accordance with the applicable PoC Criteria that a Collaboration Compound has met (i) the primary, and, if relevant, secondary endpoints regarding clinical efficacy and safety after Completion of the PoC Trial and (ii) any other PoC Criteria.

1.134 "**PoC Costs**" shall have the meaning assigned to such term in Section 1.136.

1.135 "**PoC Criteria**" shall mean the clinical and non-clinical criteria to be established by the Joint Program Subcommittee, subject to the agreement of the JSC and the final approval of GSK, to establish proof of concept for a given Development Candidate through the PoC Trial in a Program. The PoC Criteria shall set forth: (a) the [***] and relevant [***] for the PoC Trial

in such a manner that, following the PoC Trial, a determination can reasonably be made that such [***]; (b) where reasonable and appropriate, a [***]; (c) appropriate and validated [***] (d) [***] (i) which is appropriate [***] as to which there is no[***]which would prevent the compound from being developed into a [***] (*i.e.*, there is no known impediment which would render [***] the [***]) and (ii) that show [***]safety and tolerability profile in view of relevant clinical and regulatory considerations; (e) a [***] which is in a [***] that is suitable for [***] (*i.e.*, there is no known impediment which would render [***]); (f) a [***] taking into account suitable [***] who could run such [***], any such contractors to be agreed by the JSC are understood and controlled [***] is reasonable for such indication; and (g) a [***] that is consistent with the applicable Target Product Profile.

1.136 "**PoC Financial Cap**" shall mean the limitation on the total [***] costs and expenditures, including [***], all of which are specifically attributable to the PoC Trial for each Program (such costs and expenditures, the "**PoC Costs**"), which shall not exceed [***], except as provided in Section 3.5.5.

1.137 "**[***]**" shall have the meaning assigned to such term in Section 4.1.1.

1.138 "**[***] Exercise Fee**" shall have the meaning assigned to such term in Section 6.4.

1.139 "**[***] Exercise Period**" shall have the meaning assigned to such term in Section 4.2.2.

1.140 "**PoC Report Date**" shall have the meaning assigned to such term in Section 4.2.2.

1.141 "**PoC Trial**" shall mean, with respect to a Program, the first human in-patient study designed to provide evidence of efficacy, safety and tolerability of a Collaboration Compound within such Program, which if conducted by Regulus, shall be consistent with the [***]agreed upon by the Parties and the PoC Financial Cap, subject to Section 3.5.5. For purposes of clarity, the PoC Trial is intended only to demonstrate the [***] of a particular Development Candidate, and is not intended to be a [***], or intended to otherwise provide data [***].

1.142 "**PoC Trial Report**" shall have the meaning assigned to such term in Section 4.2.2.

1.143 "**Pre-Clinical Studies**" shall mean *in vitro* and *in vivo* studies of a Collaboration 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 Collaboration Compound and whether the Collaboration Compound has a desired effect.

1.144 "**Preliminary PoC Plan**" shall have the meaning assigned to such term in Section 3.4.4.

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

1.146 "**Program**" shall mean, with respect to a Collaboration Target, the Research Program and, if GSK has not exercised its [***] Option, the Early Development Program, taken together. For purposes of clarity, except as stated to the contrary in this Agreement, all references to rights and obligations in connection with a Program which has been terminated under the Agreement or with respect to which GSK has exercised a Program Option, shall refer to the continuing or surviving rights and obligations of the Parties as applicable in accordance with the relevant provisions of the Agreement with respect to Collaboration Compounds Developed under such Program, and any Derivatives of such Collaboration Compounds Developed thereafter by the Commercializing Party.

1.147 "**Program Data**" shall have the meaning assigned to such term in Section 3.7.1.

1.148 "**Program Option**" shall have the meaning assigned to such term in Section 4.1.1.

1.149 "**Program Option Exercise Fee**" shall mean either the [***] Option Exercise Fee or the [***] Exercise Fee.

1.150 "**Program-Specific Technology**" shall have the meaning assigned to such term in Section 6.8.

1.151 "**Program Term**" shall define the duration of each Program hereunder and shall be determined on a Program-by-Program basis. For each Program, the Program Term shall consist of: (a) the Research Collaboration Term and (b), if GSK has not exercised its [***] Option for such Program, the Early Development Program Term; provided, however, that the Program Term shall terminate when GSK exercises a Program Option with respect to such Program, or GSK's right to exercise the [***] with respect to such Program has expired without GSK's exercise of such Program Option, or such Program is otherwise earlier terminated.

1.152 "**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.

1.153 "**Receiving Party**" shall have the meaning assigned to such term in Section 9.1.

1.154 "**Refused Candidate**" shall have the meaning assigned to such term in Section 4.2.7.

1.155 "**Refused Candidate Product**" shall have the meaning assigned to such term in Section 4.2.7.

1.156 "**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 a particular Licensed Product in the applicable jurisdiction.

1.157 "**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 a Licensed Product in such country, and any successor(s) thereto.

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

1.159 "**Regulus Collaboration Know-How**" shall have the meaning assigned to such term in Section 8.1.2.

1.160 "**Regulus Collaboration Patents**" shall have the meaning assigned to such term in Section 8.1.2.

1.161 "**Regulus Collaboration Technology**" shall have the meaning assigned to such in Section 8.1.2.

1.162 "**Regulus Diligence Failure Event**" or "**Regulus Exclusivity Breach**" shall have the respective meanings set forth in Section 12.2.3.

1.163 "**Regulus Know-How**" shall mean:

(a) all Parent Company Know-How Controlled by Regulus or any of its Affiliates as of the Effective Date or during the Agreement Term,

(b) all Know-How, other than Parent Company Know-How, Controlled by Regulus or any of its Affiliates as of the Effective Date or during the Agreement Term (except as otherwise expressly provided herein) that relates to:

(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 a specific miRNA,

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

(vi) [***] relating to miRNA Compounds or miRNA Therapeutics (including but not limited to [***]);

provided, however, that in each case of (a) and (b), (x) for any such Know-How other than Parent Company Know-How that includes [***] and which is not [***] as defined in Section [***] the provisions of Section 6.8.2 will govern whether such Know-How will be included as Regulus Know-How, and (y) Regulus Know-How shall exclude Collaboration Know-How.

1.164 "**Regulus License Agreement**" shall have the meaning assigned to such term in the Recitals.

1.165 "**Regulus LLC Agreement**" shall have the meaning assigned to such term in the Recitals.

1.166 "**Regulus Patents**" shall mean:

(a) all Parent Company Patents Controlled by Regulus or any of its Affiliates as of the Effective Date or during the Agreement Term, including all Parent Company Patents licensed to Regulus or any of its Affiliates under the Regulus License Agreement and listed on Exhibit B,

(b) all Patent Rights, other than Parent Company Patents, owned by Regulus or any of its Affiliates as of the Effective Date and listed on Exhibit C or otherwise Controlled by Regulus or any of its Affiliates as of the Effective Date and listed on Exhibit D, and

(c) all Patent Rights, other than Parent Company Patents, Controlled by Regulus or any of its Affiliates during the Agreement Term (except as otherwise expressly provided herein) 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 [***] of the specific miRNA,

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

(vi) [***] relating to miRNA Compounds or miRNA Therapeutics (including but not limited to [***]);

1.167 provided, however, that in each case of (a) through (c), (x) for any such Patent Rights other than Parent Company Patents and which is not [***] as defined in Section [***] that include [***], the provisions of Section 6.8.2 will govern whether such Patent Right will be included as a Regulus Patent hereunder, and (y) Regulus Patents shall exclude Collaboration Patent Rights. "**Regulus Technology**" shall mean the Regulus Patents and Regulus Know-How, excluding any Collaboration Technology owned by Regulus either solely or jointly (including by assignment from any permitted subcontractor of Regulus pursuant to Section 3.10).

1.168 "**Replaceable Target**" shall have the meaning assigned to such term in Section 3.2.1.

1.169 "**Reports**" shall have the meaning assigned to such term in Section 4.2.2.

1.170 "**Research Collaboration Term**" shall define the duration of each Research Program hereunder and shall be determined on a Research Program-by-Research Program basis as follows: the period ending upon the later of (a) [***] years following the Final Target Selection Date, or (b) the date on which the activities set forth under the Research Plan for a given Research Program are all completed; provided, however, that such period shall terminate when (i) GSK exercises the relevant [***] Option, (ii) the JSC ([***] as applicable) terminates such Program, (iii) the Collaboration Compound which is the subject of such Research Program is confirmed by the JSC as a Development Candidate, or (iv) the date on which such Program is terminated earlier in accordance with the applicable provisions of this Agreement.

1.171 "Research Plan" shall mean a research plan (including any subsequent updates or amendments thereto) for each given Research Program that sets forth the outline of activities to be conducted by Regulus comprising such Research Program. Such Research Plan shall be based on the activities outlined in the Initial Research Plan.

1.172 "**Research Program**" shall mean, with respect to a Collaboration Target, the Development activities performed or to be performed by Regulus in accordance with the Research Plan during the Research Collaboration Term directed to identifying a Development Candidate for such Collaboration Target, including research, identification, characterization, optimization and pre-clinical testing of Collaboration Compounds up until initiation of a [***]

1.173 "**Returned Licensed Product**" shall have the meaning assigned to such term in Section 4.3.2.

1.174 "**Reverse Royalty**" shall have the meaning set forth in Section 6.7.

1.175 "**Royalty-Bearing Product**" shall mean (a) any Licensed Product Commercialized by or on behalf of GSK, its Affiliates or Sublicensees hereunder, upon the sale of which GSK would owe Regulus a royalty pursuant to Section 6.6; and (b) any Refused Candidate Product or Returned Licensed Product Commercialized by or on behalf of Regulus, its Affiliates or Sublicensees hereunder, upon the sale of which Regulus would owe a royalty to GSK pursuant to Section 6.7. For purposes of clarity, Royalty-Bearing Product includes the relevant Combination Products.

1.176 [***].

1.177 "**Screening Assays**" shall mean the screening assays as defined in the Initial Research Plan.

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

1.179 "**Selling Party**" shall have the meaning assigned to such term in Section 1.113.

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

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

1.182 "**Subcommittee**" shall have the meaning assigned to such term in Section 2.2.

1.183 "**Sublicensee**" shall mean a Third Party or Parent Company to whom a Party or its Affiliates or Sublicensees has granted a sublicense or license under any Collaboration Technology and/or Regulus Technology or GSK Technology, as the case may be, licensed to such Party in accordance with the terms of this Agreement.

1.184 "**Subsequent Collaboration Target**" shall have the meaning assigned to such term in Section 3.2.1.

1.185 "**Target**" shall mean a miRNA.

1.186 "**Target Product Profile**" or "**TPP**" shall mean, with respect to a given Development Candidate or class of compounds, and a given Indication, the targeted attributes for an aspirational drug product for the treatment and/or prophylaxis of such Indication. These attributes will be determined through an understanding of current and future unmet medical and market needs, and of the product performance necessary for Regulatory Approval and

competitive differentiation at the time of anticipated launch. By way of guideline only, a TPP typically contains information on at least the following parameters: [***].

1.187 "**Target Selection Period**" shall have the meaning assigned to such term in Section 3.2.1.

1.188 "**Terminated Program Option**" shall have the meaning assigned to such term in Section 4.1.1.

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

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

1.191 "**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 Collaboration Compounds and/or Licensed Products hereunder, including, without limitation, [***] 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 [***], 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 Parent 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 [***].

1.192 "**Third Party and Parent-Originated Rights and Obligations**" shall mean the rights of, and any limitations, restrictions or obligations imposed by, (a) Parent 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, [***](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)[***].

1.193 "**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 Collaboration Compounds and/or Licensed Products 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 [***] (although, for clarity, if such costs and payments are [***] 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 [***].

1.194 "**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.

1.195 "**Upfront Payment**" shall have the meaning assigned to such term in Section 6.1.

1.196 "**Valid Claim**" shall mean a claim (a) of any issued, 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; [***].

1.197 [***] shall have the meaning assigned to such term in Section 12.7.7(a).

ARTICLE 2

GOVERNANCE OF THE COLLABORATION

2.1 The Joint Steering Committee.

2.1.1 *Generally*. Promptly, and in any event within [***] days, after the Effective Date, the Parties shall establish and convene a committee (the "**Joint Steering Committee**" or "**JSC**") as more fully described in this Section 2.1. The JSC shall have review and oversight responsibilities, including the responsibilities set forth in Section 2.1.6 below, for all Development activities performed by the Parties under the Initial Research Plan, the Research Plans and, if applicable, the Early Development Plans during the Collaboration Term. After the exercise by GSK of a Program Option for a Program, the JSC shall remain in place solely to serve as a vehicle to facilitate the communication of information between the Parties with respect to any subsequent Development activities by GSK with respect to the Option Compounds and related Licensed Products Developed under such Program and, once Commercialization is underway with respect to such Program (as measured by the Regulatory Approval, in any country of the world, of a Licensed Product with respect to such Program), GSK will keep

Regulus informed of activities through an annual progress report and the JSC shall no longer be required to meet with respect to such Program. Each Party agrees to keep the JSC informed of the progress of the Development and/or Commercialization activities for which such Party is responsible hereunder with respect to each Program.

2.1.2 *Regulus' Right to Discontinue Participation*. Notwithstanding anything in this Agreement to the contrary, at any time following the end of the Program Term with respect to a Program hereunder, Regulus shall have the right, upon written notice to GSK, to discontinue its participation in the Joint Steering Committee or any Subcommittee thereof with respect to such Program, and such discontinuation by Regulus shall not constitute a breach of Regulus' obligations hereunder. For the avoidance of doubt, the exercise by Regulus of its right to discontinue its participation in the JSC pursuant to this Section 2.1.2 will not relieve Regulus of the obligation to perform any of its activities under any Program hereunder, and GSK shall have the right in such event to make decisions on matters where the JSC would have had such right and authority with respect to such Program, as necessary in order to continue such Programs. For clarity, in the event that Regulus obtains rights to Refused Candidates, Refused Candidate Products or Returned Licensed Products

hereunder, Regulus shall have the right in such event to make decisions on all matters related to the Development, Manufacture and/or Commercialization of such Refused Candidates, Refused Candidate Products or Returned Licensed Products.

2.1.3 *Membership*. The JSC shall be comprised of [***] representatives (or such other number of representatives as the Parties may agree) from each of GSK and Regulus. Each Party shall provide the other with a list of its initial members of the JSC on the Effective Date. Each Party may replace any or all of its representatives on the JSC at any time upon written notice to the other Party in accordance with Section 13.6 of this Agreement. Each representative of each Party shall be of the seniority and have expertise (either individually or collectively) in business and pharmaceutical drug discovery and development appropriate for service on the JSC in light of the functions, responsibilities and authority of the JSC and the status of Development of the Collaboration Compounds and related Licensed Products. Any member of the JSC may designate a substitute to attend and perform the functions of that member at any meeting of the JSC. Each member of the JSC, and any such substitute, shall be subject to the confidentiality obligations of Article 9. Each Party may, in its reasonable discretion, invite non-member representatives of such Party to attend meetings of the JSC as a non-voting participant, subject to the confidentiality obligations of Article 9. The Parties shall designate a chairperson (each, a "**Chairperson**") to oversee the operation of the JSC, each such

Chairperson to serve a twelve (12) month term. The right to name the Chairperson shall alternate between the Parties, with [***] designating the first such Chairperson.

2.1.4 *Meetings*. During the Collaboration Term (subject to Section 2.1.2), the JSC shall meet in person or otherwise once each Calendar Quarter, and less or more frequently as the Parties mutually deem appropriate, on such dates, and at such places and times, as provided herein or as the Parties shall agree. Upon the conclusion of the Collaboration Term (subject to Section 2.1.2), the JSC shall meet, in person or otherwise, once every two (2) Calendar Quarters or more or less frequently as mutually agreed between the Parties, to provide Regulus an update regarding GSK's efforts after exercise of its Program Option(s) and otherwise to perform the responsibilities assigned to it under this Agreement while a Collaboration Compound is in Development; provided, however, that the Parties agree to periodically discuss in good faith the frequency and scope of such ongoing meetings and such JSC meetings will not occur once all Programs are in Commercialization (as measured by the Regulatory Approval, in any country of the world, of a Licensed Product with respect to each such Program). Meetings of the JSC that are held in person shall alternate between the offices of the Parties, or such other place as the Parties may agree. The members of the JSC also may convene or be polled or consulted from time to time by means of telecommunications, video conferences, electronic mail or correspondence, as deemed necessary or appropriate.

2.1.5 *Minutes*. During the Collaboration Term (subject to Section 2.1.2), the Chairperson shall designate to the Alliance Manager of the other Party, responsibility for preparing and circulating minutes within [***] days after such meeting setting forth, a brief summary of the discussions at the meeting and a list of any actions, decisions or determinations approved by the JSC and a list of any issues to be resolved by the Executive Officers pursuant to Section 2.1.7. Such minutes shall be effective only after written approval of such minutes by both Parties. With the sole exception of specific items of the meeting minutes to which the members cannot agree and which are escalated to the Executive Officers as provided in Section 2.1.7 below, definitive minutes of all JSC meetings shall be finalized no later than [***] days after the meeting to which the minutes pertain. If at any time during the preparation and finalization of the JSC minutes, the Parties do not agree on any issue with respect to the minutes, such issue shall be resolved by the escalation process as provided in Section 2.1.7. The decision resulting from the escalation process shall be recorded by the designated Alliance Manager in amended finalized minutes for said meeting. Notwithstanding any of the foregoing, in no event shall such minutes be deemed to amend, or be incorporated into, the terms of this Agreement.

2.1.6 *Specific Responsibilities of the JSC*. Without limiting any of the foregoing, subject to Sections 2.1.7 and 2.2.2, the JSC shall perform the following functions for any given Program, some or all of which may be addressed directly at any given meeting of the JSC:

(a) Review [***] each Research Plan and any amendments thereto as it relates to either an Initial Collaboration Target or a Subsequent Collaboration Target;

(b) Confirm that the Discovery Milestone has been achieved for a Program, [***];

(c) review, update [***] (upon unanimous agreement of the Parties) the Candidate Selection Criteria within [***] days of recommendation by the JPS, including any amendments thereto proposed by either Party (through the JPS, JSC or otherwise);

(d) amend ([***] of the Parties) the Candidate Selection Criteria from time to time;

(e) confirm ([***] of the Parties) whether a Collaboration Compound meets the Candidate Selection Criteria;

(f) review, update [***] (upon unanimous agreement of the Parties) the (i) design and content of the PoC Criteria, (ii) Target Product Profile upon which such PoC Criteria was based, and (iii) design, content and endpoints of the PoC Trial, in each case within [***] days of recommendation by the JPS, including any amendments to the PoC Criteria design and content, Target Profit Profile or PoC Trial design, content and endpoints which may be proposed by either Party (through the JPS, JSC or otherwise), each of (i), (ii) and (iii) shall be subject to GSK final decision-making authority as described in Section 2.1.7(b);

(g) review the overall progress of Regulus' efforts to discover, identify, optimize and otherwise Develop Collaboration Compounds under each Program, including review and [***] of any proposal for termination of a Program;

(h) review [***] the Development of any Collaboration Compound for the treatment of any potential additional Indications;

(i) review, update [***] (upon unanimous agreement of the Parties) the Initial Research Plan, the Research Plans and, if applicable, the Early Development Plans, including any technical changes or amendments thereto which may be proposed by either Party (through the JPS, JSC or otherwise) to reflect [***], with the aim of achieving the [***] Criteria and [***] Criteria;

(j) discuss and attempt to resolve (by unanimous agreement of the Parties) any deadlock issues submitted to it by any Subcommittee, including the resolution of any disputes regarding [***]; and

(k) such other responsibilities as may be assigned to the JSC pursuant to this Agreement or as may be mutually agreed upon by the Parties from time to time;

provided, however, that in no event shall the JSC have any authority to (x) resolve any disputes involving the breach or alleged breach of this Agreement, (y) amend any budget or allocation of costs between the Parties, or require either Party to expend additional resources, whether internal or external, except as stated under this Agreement pursuant to the exercise of discretionary authority expressly granted to the JSC or (z) otherwise amend or modify this Agreement or the Parties' respective rights and obligations hereunder.

2.1.7 *Decision-Making Authority and Escalation Process*.

(a) Generally, except as otherwise expressly provided herein, all decisions of the JSC shall be made by consensus, with each Party having collectively [***] in all decisions.

(b) Prior to the exercise by GSK of its Program Option for a given Program, unless such Program is earlier terminated, if the JSC cannot agree on a matter within its purview, the matter will be escalated to the Parties' Executive Officers, who shall have a period of [***] days (unless extended by mutual agreement of the Executive Officers) to resolve such dispute by cooperating in good faith. Except as otherwise stated below in this Section 2.1.7, if the Parties still cannot agree on a matter after such escalation to the Executive Officers, the Parties will submit such matter to binding arbitration in accordance with Section 13.1; provided, however, that, in lieu of binding arbitration, (i) if the dispute relates primarily to [***], the dispute will instead be resolved by [***] in accordance with [***] and (ii) for each Program, GSK will have final decision-making authority with respect to any disputes between the Parties concerning (A) the [***], (B) the [***], and/or (C) the [***], and none of such disputes listed in [***] above will be subject to arbitration under Section 13.1 or any other form of review, provided, that, in the case of any dispute regarding (ii) above GSK asserts such final decision-making right in good faith, based upon [***] or upon some other rational basis in light of [***], and subject to Section 3.5.5 with respect to the [***].

(c) After the exercise by GSK of its Program Option for a given Program, GSK will have sole decision-making authority on all decisions relating to the Development and Commercialization of any Option Compounds and related Licensed Products

under such Program. If Regulus disagrees with any such decisions taken by GSK, such disagreement will not be escalated to the Executive Officers nor shall any such disagreement be submitted to arbitration under Section 13.1 or any other form of review; provided, however, that GSK will comply with its diligence obligations (as described below in Article 4) and other relevant obligations as expressly stated hereunder (including payment obligations) and any dispute with respect to whether there has been a material breach by GSK of such obligation may be escalated to the Executive Officers and, if the Executive Officers are unable to resolve such dispute within thirty (30) days thereof, to binding arbitration under Section 13.1.

(d) Regulus shall not have the right to progress any [***] without the express prior unanimous approval of the JSC, and shall not have the right to research or pursue any [***] for any Collaboration Compound (other than [***] applicable to such Collaboration Compound) without the express prior unanimous approval of the JSC, except with respect to Refused Candidates, Refused Candidate Products and Returned Licensed Products.

(e) Notwithstanding anything in this Agreement to the contrary, if the JSC is unable to unanimously agree on any matter before it (including the resolution of any dispute arising at any Subcommittee level), such matter shall be subject to escalation to the Executive Officers and resolution as described in this Section 2.1.7, except in the case of matters which pertain to Prosecution and Maintenance which shall be resolved in accordance with Article 8.

2.2 Subcommittee(s). From time to time, the JSC may establish subcommittees to oversee particular projects or activities, as it deems necessary or advisable (each, a "**Subcommittee**"). Each Subcommittee shall consist of such number of members as the JSC determines is appropriate from time to time. Such members shall be individuals with expertise and responsibilities in the areas relevant to the function and purpose of the proposed Subcommittee. Generally, except as otherwise expressly provided herein (including Section 2.2.2), all decisions of any Subcommittee shall be made by consensus, with each Party having collectively one (1) vote in all decisions.

2.2.1 *Joint Program Subcommittee*.

(a) Promptly after the establishment of the JSC pursuant to Section 2.1, the JSC shall establish the Joint Program Subcommittee (the "**JPS**"). The JPS shall be comprised of [***] representatives (or such other number of representatives as the Parties may agree) from each of GSK and Regulus and shall meet once every Calendar Quarter or more or less frequently as the Parties mutually agree (subject to Section 2.1.2). The JPS will report to the JSC and will be responsible for the recommendation to the JSC with respect to each Program of

(i) the Candidate Selection Criteria for such Program, which shall be recommended to the JSC no more than [***] days following the selection of the relevant Collaboration Target, (ii) the design and content of all PoC Criteria and Target Product Profiles for such Program as set forth below, which shall be recommended to the JSC no more than [***] days following the nomination of a Development Candidate, and (iii) the design, content and endpoints of all PoC Trials, which shall be recommended to the JSC no more than [***] days following the nomination of a Development Candidate. In the event of a dispute within the JPS on any matter, such matter shall be submitted to the JSC for resolution in accordance with the provisions of Section 2.1.7(b).

(b) For each Program, a Target Product Profile shall be prepared by GSK, in consultation with Regulus and through the JPS, for adoption by the Joint Steering Committee; provided, that each TPP shall (i) be consistent with and no broader than the Indication and Collaboration Targets for its corresponding Program, and (ii) set as the objective for the Program competitiveness in the applicable market, but not necessarily superiority in all aspects relevant to pharmaceutical commercialization. Upon nomination of a Development Candidate, each such aspirational TPP shall be updated, amended or modified to specifically address the particular qualities and features of such Development Candidate. In the event of a disagreement at the JSC level, GSK shall have the final decision-making authority on the content of the Target Product Profile or any amended TPP as set forth in Section 2.1.7(b). It is understood and agreed that the Target Product Profile is aspirational in nature, and that any given Development Candidate may not meet all targeted features and requirements of a given TPP, and that certain features of the TPP may only apply to later stages of Development of a given Development Candidate (such as development of a sustained release formulation, etc.).

2.2.2 *Joint Patent Subcommittee*. Promptly after the establishment of the JSC pursuant to Section 2.1, the JSC shall establish a Joint Patent Subcommittee (the "**Joint Patent Subcommittee**"). The Joint Patent Subcommittee shall be comprised of an equal number of representatives from each of GSK and Regulus. The Joint Patent Subcommittee will report to the JSC and will be responsible for the coordination of the Parties' efforts in accordance with the provisions set forth in Article 8 of this Agreement (subject to Section 2.1.2). In the event of a dispute within the Joint Patent Subcommittee, such matter shall be submitted to the JSC for resolution; provided, however, that the provisions of Article 8 shall determine which Party shall have control and the final decision-making authority with respect to matters related to Prosecution and Maintenance, enforcement of Patent Rights, the determination of inventorship, and patent listing obligations.

2.3 Alliance Managers. Promptly after the Effective Date, each Party shall appoint an individual (other than an existing member of the JSC) to act as the project leader for such Party (each, an "**Alliance Manager**"). Each Alliance Manager shall thereafter be permitted to attend meetings of the JSC and any other Subcommittee as a nonvoting observer, subject to the confidentiality provisions of Article 9. The Alliance Managers shall be the primary point of contact for the Parties regarding the activities of the Parties contemplated by this Agreement during the Agreement Term and shall facilitate all such activities hereunder, including, but not limited to, communications between the Parties following any decisions made by the JSC, and the exchange of information between the Parties as described in Section 3.9.2. The Alliance Managers shall also be responsible for assisting the JSC and the Joint Program Subcommittee in performing their respective responsibilities. The name and contact information for such Alliance Manager, as well as any replacement(s) chosen by Regulus or GSK, in each such Party's sole discretion, from time to time, shall be promptly provided to the other Party in accordance with Section 13.6 of this Agreement.

2.4 Certain Matters Subject to Expert Panel. If, at any time during the relevant Program Term, the JSC is unable to agree whether to [***], the Parties shall 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 shall promptly hold a hearing to review the matter, at which they will consider briefs submitted by each Party at least [***] 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 Programs in order to align the expertise of the members of the Expert Panels with the subject matter of the respective Programs. The Expert Panel will only [***] if the Expert Panel unanimously agrees that [***] is [***]. The Expert Panel shall not be permitted to take into account [***]. The determination of the relevant Expert Panel as to such dispute shall be binding on both Parties. The Parties shall 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.

ARTICLE 3

THE CONDUCT OF THE COLLABORATION; REGULUS DILIGENCE

3.1 Overview. Subject to and in accordance with the terms of this Agreement, Regulus will be responsible for conducting [***] Programs, each to be directed at a different Collaboration Target to be selected as set forth in Section 3.2 below, with the goal of researching, identifying and otherwise Developing [***] Collaboration Compounds under each Program through to [***], subject to earlier termination of such Program or the exercise of the [***] Option as described in this Agreement.

3.2 Selection of Targets.

3.2.1 *Initial Collaboration Targets; Subsequent Collaboration Targets*. As of the Effective Date, GSK has selected [***] Targets to be the subject of Programs to be progressed by Regulus under Section 3.3 (each such Target, an "**Initial Collaboration Target**"), which [***] Initial Collaboration Targets are listed on Exhibit E hereto. GSK shall have the right to identify an additional [***] Targets (each, a "**Subsequent Collaboration Target**", and together with the Initial Collaboration Targets, the "**Collaboration Targets**") from the miRNA Pool within [***] months of identification of such miRNA Pool from within the miRNA Library in accordance with the Initial Research Plan (such [***] period, the "**Target Selection Period**" and the end of such [***] period being the "**Final Target Selection Date**"); provided, further, that GSK may, at any time during the Target Selection Period, replace up to [***] previously-identified Collaboration Targets which have not reached [***] (each, a "**Replaceable Target**") with a different Target from the miRNA Pool, in which case, such different Target shall become a Collaboration Target and such previously-identified Collaboration Target (as such, a "**Former Target**") shall no longer be a Collaboration Target. For purposes of clarity, notwithstanding anything in this Agreement to the contrary, in no event shall GSK have the ability to replace more than [***] previously-identified Collaboration Targets under this Agreement, nor shall there be more than a total of [***] Collaboration Targets as of the Final Target Selection Date. Any Target which is not a Collaboration Target as of the Final Target Selection Date shall thereafter be a Former Target.

3.2.2 *Selection to be Completed by Final Target Selection Date*. After the selection of the Subsequent Collaboration Targets by GSK from the miRNA Pool, to be completed by the Final Target Selection Date, Regulus will progress Programs against such Subsequent Collaboration Targets in accordance with the Research Plan for each Program as set forth in Section 3.3. If any Subsequent Collaboration Target is not selected within the Target

Selection Period, GSK's rights and Regulus' obligations under the Agreement with respect to such Subsequent Collaboration Target and related Program shall terminate.

3.2.3 *Blocked Targets*. Additionally, if during the Target Selection Period, Regulus intends to work outside of the Research Program, along with or for the benefit of an Affiliate, Parent Company or a Third Party, to identify, research, optimize, otherwise Develop or Commercialize any [***] prior to the selection by GSK of all [***] final Collaboration Targets, then Regulus shall first offer in writing to GSK the right to select such miRNA as one of the remaining Collaboration Targets hereunder, including as a replacement for any Replaceable Target, in each case solely to the extent that GSK has the right to do so under Section 3.2.1 above (including the [***] limitation set forth therein), such right to expire [***] days after GSK's receipt of such written offer. If GSK does not select such miRNA as a Collaboration Target hereunder, such miRNA shall thereafter be excluded from the miRNA Pool and deemed a Blocked Target; provided, however, that no more than [***] of the number of miRNAs in the miRNA Pool may be deemed to be a Blocked Target under the Agreement.

3.2.4 *Expansion of Agreement*. The Parties hereby agree that, on or about the date that is [***] years after the Effective Date as may be mutually agreed by the Parties, the Parties shall meet to discuss and consider in good faith the possible expansion of the Agreement to include additional Targets, on [***], but without any obligation on either Party to enter into any such expanded Agreement.

3.3 Commencement of the Programs; Research Program; Research Plan.

3.3.1 *Commencement of Program*. Commencing on the Effective Date, Regulus will progress Programs directed against the Initial Collaboration Targets in accordance with the Research Plan for each such Program. The Programs directed against the Subsequent Collaboration Targets shall each commence as soon as practicable after the selection of such Subsequent Collaboration Targets and the final JSC approval of the Research Plan with respect to such Program.

3.3.2 *Research Program*. Subject to the oversight of the JSC and except as may be mutually agreed by the Parties, Regulus shall be solely responsible for conducting all Development activities set forth in the Research Plan with respect to Collaboration Compounds under each Research Program, and for all costs and expenses associated therewith, during the relevant Research Collaboration Term.

3.3.3 *Research Plan*. Each Research Program will be carried out by Regulus pursuant to a Research Plan, which will outline (subject to JSC [***] and/or amendment as set

forth in Section 2.1.6), for each Collaboration Target, as appropriate: discovery, research and optimization activities in connection with the identification and progression of Collaboration Compound to Candidate Selection Stage; and estimated timelines for completion of the studies and activities to be undertaken by Regulus thereunder. The Research Plan shall be updated by Regulus as needed, but at least once Annually and submitted to the JSC for its review and comment and may be further amended, at any time and from time to time, by Regulus, to reflect material events or changes under the then-current Research Plan. It is expected that the level of detail required for activities with respect to each Collaboration Target will vary depending on the state of progression of Regulus' efforts with regard to such Collaboration Target.

3.4 Development Candidate Selection; Preliminary PoC Plan.

3.4.1 *Selection of Development Candidate*. During the relevant Research Collaboration Term, using the Candidate Selection Criteria and Target Product Profile as a guide, Regulus shall use Diligent Efforts to conduct studies under each Research Program that it determines appropriate to Develop a Development Candidate, and to select [***] Collaboration Compound that it determines has met the Candidate Selection Criteria. Upon such determination, Regulus shall seek confirmation by the JSC that such Collaboration Compound meets the Candidate Selection Criteria. The JSC shall review all relevant information and study results concerning each such proposed Development Candidate, and, if the JSC unanimously confirms such selection, then (x) such Collaboration Compound shall be designated a Development Candidate, (y) the Parties shall agree upon an Early Development Plan for such Development Candidate, and (z) following JSC approval of such Early Development Plan, the Early Development Program for such Development Candidate shall commence in accordance with Section 3.5. If the JSC does not confirm that such Collaboration Compound meets the Candidate Selection Criteria, then the procedures set forth in Section 3.4.3 shall apply.

3.4.2 *Identification of Back-Up Compounds*. Upon JSC confirmation of a Development Candidate, Regulus may also identify Collaboration Compounds as preliminary Back-up Compounds to such Development Candidate. With respect to any Back-up Compound for such Program, if such Back-up Compound has not yet reached the [***] Stage as of the expiration of the [***] Option Exercise Period with respect to such Program, Regulus shall have the right, but not the obligation, to conduct Development activities to advance such Back-up Compound to the [***] Stage [***].

3.4.3 *If No [***] is Selected*. For clarity, if no Collaboration Compound under a Program meets the [***] Criteria, or the JSC does not confirm Regulus' nomination of a Collaboration Compound as a [***] after completion of the activities outlined in the applicable

Research Plan or otherwise decides to terminate the Program by the end of the Research Collaboration Term, the Program shall be deemed terminated by the JSC, Regulus shall not be required to conduct any activities under any Early Development Program with respect to such Collaboration Target, and the Collaboration Compounds directed against such Collaboration Target shall be deemed Refused Candidates and revert to Regulus, subject to Section 4.2.7; provided, however, that GSK shall have the right to exercise its Terminated Program Option for any Program in accordance with Section 4.2.3.

3.4.4 *Preliminary PoC Plan*. At the time of, and as part of the process of selection of the Development Candidate as provided in Section 3.4.1, the Parties, through the JSC and/or JPS, shall discuss and agree upon the appropriate preliminary development strategy and a preliminary plan for establishing PoC for such Development Candidate, including the possible trial design and protocol for the PoC Trial, and estimated associated costs and

timelines, it being understood that such trial design and timelines are merely provisional and preliminary, and are subject to modification (the "**Preliminary PoC Plan**"). Regulus shall have the right, but not the obligation, to reasonably rely on such Preliminary PoC Plan in undertaking any Phase 1 Clinical Trials of such Development Candidate under any Early Development Program for such Development Candidate. Notwithstanding the foregoing, and Regulus' discretion in the overall conduct of the Research Program and Early Development Programs, the final PoC Criteria and the final PoC Trial for such Development Candidate shall be subject to the further design of the JPS and the review and unanimous approval of the JSC as set forth in Section 2.1.6, and any disputes related thereto shall be resolved in accordance with Section 2.1.7.

3.5 Early Development Program; Early Development Plan.

3.5.1 *Early Development Program*. Unless GSK exercises its [***] Option for a given Research Program within the [***] Option Exercise Period, Regulus shall proceed with conducting Development activities directed toward progressing the Development Candidate for such Research Program through Completion of the PoC Trial, including the conduct of a Phase 1 Clinical Trial and such PoC Trial, in accordance with the Early Development Plan ("**Early Development Program**"). In such case, subject to the oversight of the JSC and except as may be mutually agreed by the Parties, Regulus shall be solely responsible for conducting all Development activities set forth in the Early Development Plan with respect to Collaboration Compounds under each Early Development Program, and for all costs and expenses associated therewith, during the Early Development Program Term. GSK, through the JSC, shall have the right to provide consultation and advice with respect to such activities, which shall be considered in good faith by Regulus.

3.5.2 *Early Development Plan*. Each Early Development Program will be carried out by Regulus pursuant to an Early Development Plan, subject to JSC approval and/or amendment as set forth in Section 2.1.6. The Early Development Plan shall be updated by Regulus as needed, but at least once Annually and submitted to the JSC for its review and comment and may be further amended, at any time and from time to time, by Regulus, to reflect material events or changes under the current Early Development Plan, subject to JSC approval and GSK final decision-making authority on the PoC Criteria and the PoC Trial design. It is expected that the level of detail required for activities with respect to each Development Candidate will vary depending on the state of progression of Regulus' efforts with regard to such Development Candidate.

3.5.3 *Substitution of Development Candidate with Back-Up Compound*. If, at any time during the Early Development Program prior to initiation of the [***], the Parties mutually agree through the JSC to substitute for the Development Candidate any Back-up Compound for further Development, including without limitation mutual agreement in good faith with respect to the [***] and GSK's ability to [***], then Regulus shall undertake such substitution and Development of the Back-up Compound upon such mutually-agreed terms.

3.5.4 *Completion of PoC Trial*. Following the conduct of the PoC Trial by Regulus for any Development Candidate, Regulus shall promptly notify GSK in writing thereof and provide to the JSC and GSK the PoC Trial Report which will initiate the [***] Exercise Period. Regulus shall endeavor in good faith to provide GSK with a reasonably accurate estimate of the time that the PoC Trial Report will be available at least [***] months in advance. In the event that such estimate of delivery date is found to be more than [***] months past the estimated date, GSK shall have a [***] extension for the time allowed hereunder to exercise the PoC Option.

3.5.5 *Conduct of PoC Trial within PoC Financial Cap*. In the event that (a) GSK, in accordance with Section 2.1.7, exercises its final decision-making authority with respect to the PoC Criteria or the design, content and end points of any PoC Trial, and the JSC agrees (such agreement not to be unreasonably withheld) that the [***] of such PoC Trial would [***] or (b) the [***] of such PoC Trial actually [***] except to the extent due to [***], then, in each case, (i) Regulus shall use its Diligent Efforts to conduct such PoC Trial and [***], the amount of such [***] to be agreed prior to the initiation of the PoC Trial (to the extent possible), and in such event any [***] on account of such PoC Trial [***] shall be [***] of GSK arising under the relevant Program hereunder, or (ii) if Regulus does not have [***] to conduct such PoC Trial which has been [***], then GSK shall either, such choice to be made at GSK's sole discretion,

(A) agree to [***] such agreement not subject to [***] in making such decision, the PoC Trial, and then [***] as would have been required of Regulus hereunder, and Regulus shall be required to [***] attributable to the PoC Trial which would have been equivalent to [***] for conducting the PoC Trial if a good-faith estimate of such [***] based on the PoC Trial design, content and end points, plus, the first [***] in PoC Costs of such PoC Trial, and [***] on account of such PoC Trial above [***] shall be [***] of GSK arising under the relevant Program hereunder or (B) revise the PoC Criteria or the design, content and end points of any PoC Trial to [***].

3.6 Regulus Diligence. The common objective of the Parties is to identify and Develop [***] Collaboration Compound for each Program for Development and Commercialization as Licensed Products containing such Collaboration Compound(s) in the Field in the Territory under the terms of this Agreement. Regulus shall use its Diligent Efforts to conduct the identification, screening, characterization, optimization and other discovery and research activities in accordance with the Initial Research Plan during the Target Selection Period, and to carry out and conduct each Research Program and Development in accordance with the Research Plan, and, if GSK has not exercised its [***] Option for such Program, each Early Development Program in accordance with the relevant Early Development Plan during the Program Term. To that end, Regulus shall dedicate to the conduct of the initial discovery and research activities under the Initial Research Plan, and the Development activities under each Program, appropriate resources and allocate personnel with an appropriate level of education, experience and training in order to achieve the objectives of this Agreement efficiently and expeditiously, which resources and personnel shall be consistent with the applicable requirements of the Initial Research Plan, the Research Plan and any Early Development Plan and shall be consistent always with the standard under this Agreement applicable to Regulus for its Diligent Efforts. For purposes of clarity, Regulus shall be deemed to have met its diligence obligation hereunder with respect to each Program (a) upon achievement of the [***] Stage if GSK exercises the relevant Program Option at the [***] Stage or (b) if GSK does not exercise the relevant Program Option before [***], upon Completion of the PoC Trial and completion of all other activities set forth in the Early Development Program; provided, however, that the Parties acknowledge that such clauses (a) and (b) may not be the only proof that Regulus has met its diligence obligations.

3.7 Specific Regulus Responsibilities. During the Program Term with respect to each Program, and consistent with and subject to the applicable Research Plan and Early Development Plan (as each such plan may be updated or amended from time to time hereunder), Regulus shall be responsible for the following activities.

3.7.1 *General*. Regulus shall use its Diligent Efforts to:

(a) conduct Development activities to identify, research, optimize, and otherwise Develop Collaboration Compounds under such Program, including, without limitation, screening for new Collaboration Compounds against the relevant Collaboration Target as necessary and conducting medicinal chemistry with respect to a potential Development Candidate under the Program with the aim of achieving Candidate Selection Criteria and PoC Criteria;

(b) if GSK has not exercised the Candidate Selection Option, conduct Pre-Clinical Studies and Clinical Studies through and including the Completion of the PoC Trial for a Development Candidate and conduct formulation development of such Development Candidate for each Program;

(c) provide to the JSC reasonable progress updates at each Calendar Quarter meeting of the JSC on the status of each Program, summaries of data associated with Regulus' Development activities ("**Program Data**"), and the likelihood of and general timetable for completion of such Development activities and advancement of Collaboration Compounds to the next phase of Development, as applicable;

(d) consider in good faith all reasonable suggestions received from GSK regarding the Initial Research Plan and any Research Plan, Research Program, Early Development Plan and/or Early Development Program; and

(e) perform such other obligations with respect to each Research Program and each Early Development Program as the JSC may assign to Regulus from time to time under the Initial Research Plan and any Research Plan, Research Program, Early Development Plan and/or Early Development Program.

3.7.2 *Data Integrity***.**

(a) Regulus acknowledges the importance to GSK of ensuring that the activities under the Initial Research Plan, Research Programs and any Early Development 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, Regulus' 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) Regulus agrees that it shall carry out the Research Programs, Initial Research Plan, and the Early Development Programs and collect and record any data generated therefrom in a manner consistent with the above requirements as set forth in (a) above, and shall, upon reasonable request by GSK, permit review of relevant notebooks and records as needed as a result of GSK responsibilities under Article 8 in relation to Prosecution and Maintenance.

3.7.3 *Regulatory Matters.* During the Collaboration Term, with respect to any Program for which the Program Options have not yet been exercised or expired and which Program has not otherwise been terminated, and the Collaboration Compounds therein, Regulus shall use its Diligent Efforts to:

(a) own and maintain all regulatory filings filed by or on behalf of Regulus for Collaboration Compounds Developed pursuant to this Agreement, including all INDs filed by Regulus. Upon exercise by GSK of its Program Option with respect to a Program, Regulus shall transfer to GSK ownership of such regulatory filings for all Option Compounds Developed under such Program, as further described in Section 5.3;

(b) report all adverse drug reaction experiences related to Collaboration Compounds in connection with the activities of Regulus under this Agreement to the appropriate Regulatory Authorities in the countries in the Territory in which such Collaboration Compounds are being Developed, in accordance with the applicable laws and regulations of the relevant countries and Regulatory Authorities, and to provide GSK notice of such event and provide copies of all reports to GSK as promptly as practicable, which GSK shall use solely for purposes of facilitating GSK's decision-making with respect to its exercise of any relevant Program Option hereunder, and for no other purpose unless and until GSK exercises such Program Option. Through the JSC, GSK shall have the right, upon reasonable request, to review from time to time Regulus' pharmacovigilance policies and procedures. GSK and

Regulus agree to cooperate and use good faith efforts to ensure that Regulus' adverse event database is organized in a format that is reasonably compatible with GSK's adverse event databases. The Parties will consider in good faith from time to time whether a safety data exchange agreement is required.

3.7.4 *Manufacturing Obligations*. Regulus shall [***] use its Diligent Efforts to manufacture pre-clinical supplies and clinical supplies of Collaboration Compounds, including all bulk drug substance, for all Pre-Clinical Studies and Clinical Studies, including process development and scale-up, conducted by Regulus under such Program during the Program Term for such Program. At GSK's request, Regulus shall also supply to GSK reasonable (as determined by the Joint Steering Committee) quantities of bulk drug substance for Collaboration Compounds as reasonably required by GSK for certain supplemental Enabling Studies which GSK may from time to time undertake pursuant to Section 3.8, unless Regulus is unable to do so due to [***], provided, that the determination of whether [***] shall not take into account [***]. Regulus shall carry out its manufacturing obligations consistent with Regulus' reasonable internal practices, industry standards, cGMP requirements, and all applicable laws and regulations. For purposes of clarity, upon GSK's exercise of its Program Option for a Program, GSK will thereafter be responsible for manufacturing, [***] all pre-clinical, clinical and commercial supplies of the Option Compounds and related Licensed Products under such Program, as set forth in Section 4.4.2. The Parties shall discuss in good faith at the JSC the manufacturing process as then being used or planned to be used by Regulus for Collaboration Compounds under each Program well in advance of the Program reaching the Candidate Selection Stage, in order that, wherever practical, (a) the Parties can plan together to minimize [***], and (b) the Parties can [***] for Commercialization by GSK in the event that GSK exercises its Program Option.

3.8 GSK Enabling Studies. GSK shall have the right at all times during the Research Collaboration Term and during any relevant Early Development Program Term, to conduct, at its sole cost and expense, certain reasonable supplemental enabling activities such as additional formulation development, additional pre-clinical animal studies and/or compound scale-up ("**Enabling Studies**") which GSK reasonably deems as useful for supplementing pre-clinical and/or clinical activities conducted by Regulus pursuant to the Research Program and the Early Development Program and relating to one or more of the Collaboration Compounds. At GSK's request, Regulus shall offer GSK reasonable cooperation in relation to such Enabling Studies, including, subject to availability and Section 3.7.4, the transfer of reasonable quantities of Collaboration Compounds, if necessary. It is understood and agreed by the Parties that any such supplemental Enabling Studies are to be conducted by GSK in its reasonable discretion and not

as part of any Program, Pre-Clinical Study, PoC Trial or other Clinical Study conducted by Regulus and that Regulus shall not be permitted or required to delay the progress of any Research Program or Early Development Program to await the results of any such supplemental Enabling Studies or to transfer any responsibility to GSK for the conduct of any activities under the Research Plan or Early Development Plan and that GSK shall not be permitted (without Regulus' consent) to transfer any responsibility to Regulus for the conduct of any Enabling Studies.

3.9 Cooperation; Exchange of Information.

3.9.1 *Cooperation*. The Parties agree to cooperate in good faith during the Collaboration Term in identifying and implementing opportunities to reduce the costs incurred in the conduct of the Programs, including costs of equipment, consumables such as laboratory supplies, and Third Party services such as toxicology, clinical studies, drug substance and drug product process development, or manufacturing services, provided, that such cooperation does not delay or hamper Regulus in the performance of its activities thereunder and in no event shall Regulus be obligated to incur additional costs or expenses as a result of such new opportunities. These attempts may include exploration of [***].

3.9.2 *Exchange of Information*. During the Research Collaboration Term and the Early Development Term, Regulus shall provide to the JSC reasonable progress updates at each Calendar Quarter meeting of the JSC on the status of the Research Program for each Collaboration Target and of the Early Development Programs, summaries of data associated with Regulus' research and development efforts and the likelihood of and timetable for completion of the respective Programs or Development activities and advancement of Collaboration Compounds to the next phase of research or Development, as applicable. Any such written summaries shall be provided to JSC members at least [***] Business Days in advance of the upcoming JSC meeting. Regulus will use Diligent Efforts to share any data or information, as well as any correspondence received from or submitted to any Regulatory Authority, directly relating to Collaboration Compounds that is generated in the course of Regulus' activities hereunder, with the JSC, on an ongoing basis, regardless of whether such data or information would have a positive, neutral or negative impact on the potential commercial, scientific or strategic value of such Collaboration Compounds, in order to facilitate GSK's decision-making in connection with the exercise of an applicable Program Option and to monitor Regulus' obligations during the applicable Program Term. The provision of all such data or information shall be performed in a timely matter to accommodate all regulatory deadlines and ensure compliance with the timelines set forth in any agreed plan.

3.9.3 *Publication of Clinical Trials Results.* Each of GSK and Regulus shall have the right to publish summaries of results from any human clinical trials conducted by such Party under this Agreement, without requiring the consent of the other Party; provided however that GSK shall have no right, without the consent of Regulus, to so publish data generated by Regulus prior to GSK's exercise of its Program Option with respect to the relevant Collaboration Compounds, and, after the exercise of its Program Option, GSK shall have the right to so publish any such existing and future data generated by Regulus or GSK with respect to the relevant Collaboration Compound(s) without obtaining the consent of Regulus except with respect to any Refused Candidates, Refused Candidate Products or Returned Licensed Products. In addition, after the exercise of its Program Option by GSK, Regulus shall not have the right to publish any of such data, without the prior consent of GSK, for any data pertaining to the relevant Collaboration Compounds, except (a) with respect to any Refused Candidates, Refused Candidate Products or Returned Licensed Products and (b) as described in Section 9.2(ii). The Parties shall 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 shall provide the other Party via submission to the Joint Patent Subcommittee established under Section 2.2.2, at least [***] days prior notice to review the clinical trials results to be published for the purposes of preparing any necessary Patent Right filings.

3.10 Subcontracting. Each Party shall have the right to engage Third Party subcontractors and, in the case of Regulus, its Parent Companies, to perform certain of its obligations under this Agreement; provided that Regulus shall not have the right to subcontract, in whole or in part, the discovery, research or optimization of miRNA Antagonists against Collaboration Targets except to its Parent Companies pursuant to the Services Agreement. Any subcontractor to be engaged by a Party to perform a Party's obligations set forth in the Agreement shall 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) shall remain responsible and obligated for such activities and

shall in all cases retain or obtain exclusive [***], at the sole cost and expense of the Party engaging such subcontractor, and any such costs and expenses [***], unless the JSC agrees, in advance as documented in the relevant meeting minutes, to engage such subcontractor and to assume the proposed financial obligations that would result under any agreement with such subcontractor, in which case the allocation of such costs and expenses between the Parties shall be governed by [***]. To the extent that such exclusive [***] cannot be obtained by Regulus with respect to

[***] of Regulus, prior to entering into any such arrangement with any such subcontractor, Regulus shall 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 3.10 shall not apply to restrict or otherwise limit the rights of GSK to use a subcontractor after the exercise of its Program Option or the acquisition of exclusive rights to the Collaboration Compounds of a Program pursuant to the express provisions of Article 12 for the relevant Program beyond the restrictions and limitations expressly stated in Section 5.2.2.

ARTICLE 4

GSK'S PROGRAM OPTION RIGHTS; EXERCISE OF PROGRAM OPTIONS; GSK DILIGENCE

4.1 Program Options.

4.1.1 *Program Options*. For each Program, Regulus hereby grants to GSK the exclusive right, exercisable in accordance with this Article 4, to assume the Development, Manufacture and Commercialization of Collaboration Compounds Developed under such Program and to obtain the licenses described in Section 5.2 under the terms and conditions set forth in this Agreement (each, a "**Program Option**"), which right is exercisable, at GSK's sole discretion in accordance with the procedures set forth below, (a) at the [***] Stage ("**[***] Option**"), (b) if GSK does not exercise its Candidate Selection Option for a Program, upon Completion of the PoC Trial (the "**[***] Option**") which may include GSK's immediate termination of the Leading Compound in accordance with Section 4.2.4, (c) upon termination of such Program by the JSC [***], or otherwise for a termination of such Program pursuant to Section 3.4.3 on or before the Completion of the PoC Trial (the "**Terminated Program Option**"), or (d) as provided in Section 4.2.5. For the sake of clarity, the Program Option may be exercised once per Program, and, upon such exercise, all Collaboration Compounds under such Program are licensed to GSK under the terms and conditions set forth in this Agreement. GSK may exercise a Program Option as permitted herein by providing written notice thereof to Regulus.

4.1.2 *Upon Exercise of Program Option*. Upon exercise of a Program Option for a Program and payment of the Program Option Exercise Fee as set forth in Article 6 (as applicable), GSK shall receive the license grant described in Section 5.2 for all Collaboration Compounds which were Developed pursuant to such Program and GSK shall be responsible for

the milestone and royalty payments described in Article 6 with respect to such Collaboration Compounds and related Licensed Products and for diligence obligations with respect thereto as set forth in Section 4.4.

4.1.3 During the relevant Program Term, Regulus will not grant to any Third Party or to any of its Parent Companies rights to any Regulus Technology which are inconsistent with or which would interfere with the grant of the licenses resulting from the exercise of the Program Options to GSK hereunder. For the avoidance of doubt, the Parties understand and agree that GSK's Program Option rights, as described herein, shall be exclusive options over the Collaboration Compounds that are the subject of a given Research Program and/or Early Development Program, and unless and until such time (if any) as GSK declines to exercise or permits to lapse all of its pending or outstanding Program Option rights with respect to any such Research Program or Early Development Programs or the relevant Program is otherwise terminated, Regulus shall not have the right to offer or negotiate with any Third Party or any of its Parent Companies with respect to the grant to such Third Party or Parent Company of any right or license or other encumbrance of any kind in or to any of such Collaboration Compounds.

4.2 Exercise of Program Options.

4.2.1 *[***] Option*.

(a) On a Program-by-Program basis, Regulus will notify GSK, through the JSC, when it has Developed a Collaboration Compound that meets the [***] Criteria for nomination as a Development Candidate, and shall provide to GSK, through the JSC, within [***] days of such occurrence (to be reasonably extended if impractical depending on the nature of the Pre-Clinical Studies and the data generated thereunder), a complete data package containing all material analysis, results and preclinical data or any related material correspondence or information received from or sent to any Regulatory Authority relating to the Collaboration Compounds at issue (the "**Candidate Selection Report**"), in each case as would be reasonably expected to be material to assist and enable GSK to make its decision on whether to elect to exercise its [***] Option with respect to the Program under which such Development Candidate is Developed. In addition, GSK shall have the right to review, to the extent practical and reasonable, the original records and documentation containing such material data, results and information. The JSC shall confirm whether the [***] Criteria have been met.

(b) GSK may exercise its [***] Option with respect to a Program by delivering to Regulus a written notice of exercise not later than [***] days (unless extended by the mutual written agreement of the Parties or as permitted herein pending HSR clearance by the FTC as set forth in Section 4.2.6) after the date of receipt by GSK from Regulus of the

completed [***] Report (such [***]-day period, as it may be extended, the "**[***] Option Exercise Period**"), with respect to the Collaboration Compound at issue (such date of receipt by GSK, the "**[***] Report Date**"), specifying the Program for which the Program Option is being exercised. After providing to Regulus such written notice of its election to exercise the [***] Option, GSK shall, within [***] days of receipt of an invoice therefore from Regulus, pay the [***] Option Exercise Fee. Notwithstanding the foregoing, in GSK's sole discretion, it shall have the right to exercise a Program Option prior to the [***] Report Date but during the [***] Option Exercise Period by providing Regulus written notice thereof, in which case the Table 1 Rates will still apply to the milestone payments and royalties owed by GSK to Regulus hereunder.

(c) Notwithstanding any of the foregoing, if, at any time during the Research Collaboration Term for a Research Program, the JSC (by mutual agreement) or GSK requests that Regulus begin a [***] of a Collaboration Compound under such Research Program prior to Regulus' notification to GSK of a Collaboration Compound that meets the [***] Criteria, the [***] Criteria shall be deemed to have been met and, upon such request, the [***] Option Exercise Period shall begin.

4.2.2 *PoC Option.*

(a) If GSK does not exercise the [***] Option within the [***] Option Exercise Period, then, on a Program-by-Program basis, Regulus will continue to use Diligent Efforts to progress the Program through to the [***]. On a Program-by-Program basis, Regulus will notify GSK when it has completed a PoC Trial with respect to a Development Candidate, and shall provide to GSK, within [***] days of such occurrence (to be reasonably extended if impractical depending on the nature of the Clinical Studies, Pre-Clinical Studies and the other data generated thereunder), 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 the Development Candidate at issue (which data package need not include any information or data generated in the course of GSK's conduct of the PoC Trial, or portion thereof, under Section 3.5.5) (the "**[***] Report**", and referred to collectively with the [***] Report as the "**Reports**"), in each case as would be reasonably expected to be material to assist and enable GSK to make its decision on whether to elect to exercise its [***] with respect to the Program under which such Development Candidate is Developed. In addition, GSK shall have the right to review, to the extent practical and reasonable, the original records and documentation containing such material data, results and information.

(b) GSK may exercise its [***] with respect to a Program by delivering to Regulus a written notice of exercise, not later than [***] days (unless extended by the mutual written agreement of the Parties or as permitted herein pending HSR clearance by the FTC as set forth in Section 4.2.6) after the date of receipt by GSK from Regulus of the PoC Trial Report (such [***]-day period, as it may be extended, the "**[***] Exercise Period**"), with respect to the applicable Development Candidate at issue (such date of receipt by GSK, the "**[***] Date**"), specifying the Program for which the Program Option is being exercised, subject to the tolling of such payment obligation pursuant to Section 4.2.6. After providing to Regulus such written notice of its election to exercise the [***], GSK shall, within [***] days of receipt of an invoice therefore from Regulus, pay the [***] Exercise Fee as described in Section 6.4. Notwithstanding the foregoing, in GSK's sole discretion, it shall have the right to exercise a Program Option prior to the [***] Date by providing Regulus written notice thereof.

4.2.3 *Terminated Program Option.* Subject to GSK's obligation to pay milestones and royalties pursuant to Section 6.4, subject to Section 6.5.3, Section 6.6.1(d) and Section 6.6.2, GSK shall have the right to exercise its Terminated Program Option for a Program by providing Regulus written notice within an exercise period of [***] days (extendable to [***] days at GSK's request if made within such initial [***] day period) after the provision of a data package to GSK by Regulus (comparable to the [***] Report) for a terminated Program in accordance with GSK's Terminated Program Options as described under Section 4.1.1 (the "**Terminated Program Option Report**"); provided, that GSK's obligation to pay Regulus milestones and royalties shall vary, as set forth in Section 6.4, subject to Section 6.5.3, Section 6.6.1(d) and Section 6.6.2, depending on the stage of Development at which the termination occurred.

4.2.4 *Program Option Upon Completion of the [***] where the Leading Compound is immediately terminated.* If GSK exercises its Program Option in accordance with Section 4.2.2 after Completion of the [***] for a Leading Compound under a Program but immediately terminates the Leading Compound in order to progress a Back-up Compound under the same Program (provided that GSK provides written notice to Regulus of such decision along with or within [***] Business Days of notice of GSK's exercise of its Program Option), then GSK shall pay Regulus the royalties and milestones in accordance with the applicable [***] provided, however, that, if GSK later undertakes the Development or Commercialization of such terminated Leading Compound, then GSK shall thereafter pay Regulus the applicable royalties and milestones in accordance with the [***] with respect to all Licensed Products under the relevant Program, except that, with respect to any Milestone Event which had already been achieved by a Back-up Compound under such Program for which GSK had already paid Regulus

the relevant milestone payment in accordance with the [***], then, as such terminated Leading Compound (or another Option Compound) achieves such Milestone Event, GSK shall pay to Regulus the difference between the [***] and the [***] with respect to such Milestone Event.

4.2.5 *Early Program Option Exercise.* For purposes of clarity, upon exercise of any Program Option by GSK hereunder, GSK shall pay Regulus the Program Option Exercise Fee applicable to the exercise of such Program Option (as applicable), in addition to any other milestones and royalties which may be due in the future as a result of the Development and/or Commercialization of the Option Compounds and related Licensed Products by GSK and/or its Affiliates and Sublicensees. Notwithstanding any of the foregoing, regardless of whether or not the Development activities or stages necessary to trigger a particular Program Option for a Program have been completed or achieved (*e.g.*, regardless of whether a Collaboration Compound Developed under a Program has qualified as a Development Candidate or has satisfied the [***] Criteria, or [***] has occurred for such Collaboration Compound), GSK shall have the right, at any time prior to the completion of such Development activities which might otherwise trigger a particular Program Option (but in no event after the end of the Option Period that would otherwise apply with respect to such Program Option), to exercise its Program Option early for such Program by paying Regulus (or its successors or assigns) the Program Option Exercise Fee in accordance with the provisions of Section 6.5.5 depending upon the time at which GSK exercises its Program Option and the remaining milestone and royalty obligations shall be payable in accordance with Section 6.5.5, Section 6.6.1(f) and Section 6.6.2, depending on the time that GSK exercises its Program Option.

4.2.6 *HSR; Option Period Extension.* In the event that GSK reasonably determines in good faith that the exercise of any Program Option by GSK under this Agreement requires a filing with the Federal Trade Commission and the Department of Justice, as applicable, (collectively, the "**FTC**")

under the Hart-Scott-Rodino Antitrust Improvements Act of 1976 (15 U.S.C. §18a) ("**HSR**"), or any successor thereto or under any similar premerger notification provision in the EU or other jurisdiction, GSK shall make such filing [***], and the Option Period applicable to such Program Option shall be extended automatically for [***] from the expiration of the original Option Period (the "**Option Period Extension**") in the event that: (a) the HSR initial waiting period is still pending upon expiration of the original Option Period; or (b) a "Second Request" that GSK intends to respond to is received from the FTC in connection with such filing and final clearance has not been granted upon expiration of the Option Period; provided, that if the HSR initial waiting period ends during the original Option Period, such Option Period shall be extended for no more than an additional [***] following the end of such HSR initial waiting period. During such Option Period Extension, all rights and

obligations of the respective Parties related to the exercise of such Program Option or to make any otherwise required Program Option Exercise Fee payment shall be tolled. In the event that HSR clearance has still not been granted upon expiration of the Option Period Extension, Regulus and GSK shall promptly meet to discuss in good faith whether an additional extension of the Option Period is reasonable, with the presumption being that the Option Period shall be extended for no more than an additional [***] period, unless there is no [***], in which case no such extension shall be granted.

4.2.7 *Refused Candidates.* If GSK does not exercise its Program Option for a Program when triggered within the applicable Option Period, as may be extended by Section 4.2.6 or by the mutual written agreement of the Parties, and GSK has not exercised its Program Option early pursuant to Section 4.2.5, and does not exercise any of its Terminated Program Options under Section 4.2.3, then such Program Option shall expire with respect to such Program and except if the expired Program Option is a [***] Option (in which event Section 4.2.2(a) shall apply), and then, except if GSK acquires exclusive license rights to the relevant Collaboration Compounds under the applicable termination provisions of Article 12, any Collaboration Compounds resulting from such Program shall be referred to as "**Refused Candidates**" and any Licensed Products having any such Refused Candidate(s) as an active pharmaceutical ingredient(s) as "**Refused Candidate Products**" and GSK shall no longer have any rights with respect to such Refused Candidates and Refused Candidate Products. Regulus will thereafter have all rights as set forth in Section 12.1.5(c), itself or with a Third Party or through a Sublicensee and without regard to Article 7 (except to the extent set forth in Section 12.1.5(c)), to Develop, Manufacture and Commercialize the Refused Candidates and any Refused Candidate Products at Regulus' sole expense, and Regulus shall no longer have any obligations with respect to such Refused Candidates and any Refused Candidate Products other than the Reverse Royalty payment obligation to GSK as set forth in Section 6.7 and Section 12.1.5(c). In addition, Regulus will take responsibility for all licensing costs and payments incurred by GSK after the date that such Collaboration Compounds became Refused Candidates or Refused Candidate Products and that are owed by GSK to Third Parties (excluding any costs that were already due as payable by GSK as of the date that such Collaboration Compounds became Refused Candidates or Refused Candidate Products) as a result of the practice of intellectual property licensed from any such Third Parties in the Development, Manufacture and/or Commercialization of Refused Candidates and Refused Candidate Products hereunder, including, without limitation, all upfront fees, annual payments, milestone payments and royalty payments to the extent allocable to such Refused Candidates and Refused Candidate Products. For clarity, any such costs and payments shall only include the share of such costs and payments

attributable to such Refused Candidates and Refused Candidate Products and not to any other compounds licensed by GSK. For purposes of clarity, upon reversion of such rights to Regulus with respect to any Refused Candidates or Refused Candidate Products hereunder, such Refused Candidates shall no longer be deemed Option Compounds and/or Collaboration Compounds and such Refused Candidate Products shall no longer be deemed Licensed Products, in each case to which GSK has any rights under this Agreement, except that, upon the exercise by GSK of any Terminated Program Option under Section 4.2.3 or early exercise of a Program Option under Section 4.2.5, this Section 4.2.7 shall not apply.

4.2.8 *Right to Exercise Program Options for Development Candidates after Expiration of the Research Collaboration Term*. For clarity, it is understood and agreed by the Parties that, with respect to each Collaboration Target, GSK's rights to exercise its Program Option with respect to any Collaboration Compounds that are at the [***] Stage or later but have not yet completed or entered an Early Development Program at the time of expiration of the Research Collaboration Term, shall remain exercisable in accordance with this Article 4 until termination of the last to expire Option Period with respect to such Program, unless such Program is earlier terminated as provided hereunder.

4.3 Activities Post-Option Exercise by GSK.

4.3.1 *Commencement of Activities.* As soon as practicable after the exercise by GSK of a Program Option for a Program and receipt from Regulus of the information and materials set forth in Sections 5.3.1 and 5.3.2, GSK shall promptly commence and pursue a program of ongoing Development and Commercialization for the Option Compounds under such Program, in accordance with GSK's diligence obligations set forth below. GSK shall be solely responsible for all Development and Commercialization activities, and for all [***] associated therewith, with respect to the Development, Manufacture and Commercialization of Option Compounds and related Licensed Products of a Program, following exercise of its Program Option for such Program.

4.3.2 *Returned Licensed Products*. In the event that GSK exercises its Program Option for a Program and thereafter determines in good faith, for any reason, to cease the Development and Commercialization of all Option Compounds and related Licensed Products, on a Collaboration Target-by-Collaboration Target basis, or GSK's rights to such Option Compounds and related Licensed Products terminates for any reason other than as a result of the termination of this Agreement by GSK for Regulus' uncured material breach under Section 12.2 or for Regulus' insolvency under Section 12.6, or a termination by the JSC [***] for scientific or safety concerns pursuant to Section 12.5, then each Option Compound and related Licensed

Product resulting from such Program shall thereafter be referred to as a "**Returned Licensed Product**", and GSK shall no longer have any rights with respect to such Returned Licensed Product, except for the right to receive Reverse Royalties under Section 6.7 (except to the extent otherwise expressly set forth in Article 12). Regulus will thereafter have all rights as set forth in Section 12.7.1, 12.7.2 or 12.7.4, as applicable, itself or with a Third Party or through a Sublicensee and without regard to Article 7, to Develop, Manufacture and Commercialize the Returned Licensed Products at Regulus' sole expense, and Regulus shall have no obligations with respect to such Returned Licensed Products other than the Reverse Royalty payment obligation to GSK as set forth in Section 6.7 (except to the extent otherwise expressly set forth in Article 12). In addition, Regulus will take responsibility for all licensing costs and payments

incurred by GSK after the date that such Collaboration Compounds became Returned Licensed Products and that are owed by GSK to Third Parties (excluding any costs that were already due as payable by GSK as of the date that such Collaboration Compounds became Returned Licensed Products) as a result of the practice of intellectual property licensed from any such Third Party in the Development, Manufacture and/or Commercialization of Returned Licensed Products hereunder, including, without limitation, all upfront fees, annual payments, milestone payments and royalty payments to the extent allocable to such Returned Licensed Product. For clarity, any such costs and payments shall only include the share of such costs and payments which is attributable directly to such Returned Licensed Products and not to any other compounds licensed by GSK. For purposes of clarity, upon reversion of such rights to Regulus with respect to any Returned Licensed Products hereunder, such Returned Licensed Products shall no longer be deemed Option Compounds and/or Licensed Product to which GSK has any rights under this Agreement. For purposes of clarity, upon the exercise by GSK of any Terminated Program Option under Section 4.2.3, or the termination of a Program otherwise under Section 3.4.3 or the early exercise of a Program Option under Section 4.2.5, this Section 4.3.2 shall not apply.

4.4 GSK Diligence; Responsibilities.

4.4.1 *GSK Diligence*. GSK shall exercise its Diligent Efforts in Developing and Commercializing at least one Licensed Product in the Field [***] for each Program for which GSK exercises the Program Option. For purposes of clarity, (a) GSK shall not be required to Develop and Commercialize, with respect to a Program, more than one Option Compound resulting from a Program, provided, that GSK exerts its Diligent Efforts to Develop and Commercialize at least one Option Compound resulting from such Program, and (b) following GSK's exercise of its Program Option for a Program, GSK may, in its sole discretion, substitute the Leading Compound with another Option Compound Developed in the same Program or Develop and Commercialize other Option Compounds resulting from such Program, provided,

that GSK exerts Diligent Efforts to Develop and Commercialize such Back-up Compound or other Option Compound as the new Leading Compound in a manner that is consistent always with the standard under this Agreement applicable to GSK for its Diligent Efforts. Notwithstanding the above or any provision or interpretation of this Agreement to the contrary, GSK shall have no obligation to exercise its Diligent Efforts with respect to any Program for which GSK has exercised a Terminated Program Option or which has otherwise been terminated and to which GSK acquires exclusive rights to Develop and Commercialize the Collaboration Compounds resulting from such Program under Article 12.

4.4.2 *Specific GSK Responsibilities*. Without limiting any of the foregoing, following the exercise of a Program Option for a Program hereunder, GSK shall use its Diligent Efforts to:

(a) conduct all Pre-Clinical Studies and Clinical Studies on the Option Compounds, as deemed necessary or desirable by GSK, in accordance with this Section 4.4.2;

(b) conduct additional formulation Development of the Option Compounds as and if deemed necessary or appropriate by GSK;

(c) provide to the JSC reasonable progress updates at each regular meeting of the JSC on the status of GSK's Development efforts with respect to the Option Compounds and related Licensed Products;

(d) prepare and file all regulatory filings for the Option Compounds or related Licensed Products, including all NDAs;

(e) Manufacture or have Manufactured (including process development and scale up) all bulk drug substance or drug product material with respect to the Option Compounds and related Licensed Products for ongoing Development and Commercialization requirements, consistent with GSK's reasonable internal practices, industry standards and all applicable laws and regulations;

(f) own and maintain all NDAs, Regulatory Approvals and other regulatory filings and approvals, and all brands and trademarks for any resulting Licensed Products in the Field in the Territory;

(g) maintain a safety database with respect to all Option Compounds and related Licensed Products Developed and Commercialized by GSK, and report all adverse drug reaction experiences related to such Option Compounds and Licensed Products in connection with the activities of GSK under this Agreement to the appropriate Regulatory Authorities in the countries in the Territory in which the Option Compounds and Licensed

Products are being Developed and Commercialized, in accordance with applicable laws and regulations of the relevant countries and Regulatory Authorities and in accordance with GSK's internal policies; and

(h) conduct, at [***] all Commercialization activities in connection with the sales of Licensed Products.

ARTICLE 5

GRANT OF LICENSE RIGHTS; TECHNOLOGY TRANSFER

5.1 License Grants to Regulus.

5.1.1 *Development License*. GSK hereby grants to Regulus a [***] license, which shall not be sublicenseable without the prior written consent of GSK (except such consent shall not be required for a sublicense to the Parent Companies solely to the extent necessary for Regulus to perform its obligations for a Program hereunder), under the GSK Technology and GSK's rights to the Collaboration Technology, solely to the extent necessary for Regulus to perform its obligations hereunder during the Collaboration Term.

5.1.2 *License to Refused Candidates and Refused Candidate Products*. GSK hereby grants to Regulus, (a) subject to obtaining HSR clearance (if Regulus reasonably determines in good faith that such grant of license requires an HSR filing), (b) conditional upon (i) the expiration of all applicable Program Options without GSK's exercise thereof as set forth in Section 4.2.7, and subject to the payment by Regulus of the Reverse Royalty to GSK as set forth in Section 12.1.5(c), or (ii) the termination of the Agreement with respect to any Program(s) without GSK's exercise of any Program Options for such Program(s) on or before the end of the applicable [***] Option Exercise Period, by GSK pursuant to Section 12.3 or by Regulus pursuant to Section 12.2, 12.4 or 12.6, and subject to the payment by Regulus of the Reverse Royalty to GSK as set forth in Section 12.7.1, 12.7.2, 12.7.4 or 12.7.7, as applicable, and (c) subject to Section 12.7.4(b), an exclusive license in the relevant country(ies) of the Territory, as applicable, under the GSK Technology which was used in connection with the Program, if any (unless the Parties have mutually agreed to exclude it), and any GSK Technology covering a [***] with respect to a specific Collaboration Target that is the subject of such Program, and GSK's rights to the Collaboration Technology, solely to the extent necessary to Develop, Manufacture and Commercialize all Refused Candidates and Refused Candidate Products in the Field in the Territory. The license granted under this Section 5.1.2 shall [***] by Regulus (in accordance with Section [***], its Affiliates and Sublicensees in connection with the

further Development, Manufacture or Commercialization of such Refused Candidates and Refused Candidate Products.

5.1.3 *License to Returned Licensed Products*. GSK hereby grants to Regulus, (a) subject to obtaining HSR clearance (if Regulus reasonably determines in good faith that such grant of license requires an HSR filing), (b) conditional upon the termination of the Agreement with respect to any Program(s) after the exercise by GSK of its Program Option with respect to such Program on or before the end of the applicable PoC Program Option Exercise Period, by GSK pursuant to Section 12.3 or by Regulus pursuant to Section 12.2, 12.4 or 12.6, and subject to the payment by Regulus of the Reverse Royalty to GSK as set forth in Section 12.7.1, 12.7.2, 12.7.4 or 12.7.7, as applicable, and (c) subject to Section 12.7.4(b), an exclusive license in the relevant country(ies) of the Territory, as applicable, under the GSK Technology which was used in connection with the Program or in connection with the Option Compounds or Licensed Products resulting from the Program, if any (unless the Parties have mutually agreed to exclude it), and any GSK Technology covering a [***] with respect to a specific Collaboration Target that is the subject of such Program, and GSK's rights to the Collaboration Technology, solely to the extent necessary to Develop, Manufacture and Commercialize all Returned Licensed Products in the Field in the Territory. The license granted under this Section 5.1.3 shall be [***] by Regulus (in accordance with Section [***]), its Affiliates and Sublicensees in connection with the further Development, Manufacture or Commercialization of such Returned Licensed Products. For clarity, this provision shall not apply to any scenario wherein, as the result of termination of a Program under the applicable provisions of Article 12, GSK obtains exclusive license rights to the relevant Collaboration Compounds of a Program.

5.1.4 *Sublicense Rights.* As set forth in Sections 5[***] subject to Section 12.7.4(b), Regulus shall have the right to grant certain sublicenses; provided, that, each such sublicense shall be subject and subordinate to, and consistent with, the applicable terms and conditions of this Agreement. Regulus shall provide GSK with a copy of any sublicense granted pursuant to Sections 5.1.2 or 5.1.3 within thirty (30) days after the execution thereof. Such copy may be redacted to exclude confidential scientific information and other information required by a Sublicensee to be kept confidential; provided, that for Agreements entered into by Regulus after the Effective Date, [***], Regulus will [***] obtain the consent to disclose relevant material financial terms and material non-technical information to the extent required by GSK. GSK may share such copy or information with its Affiliates and relevant Third Party licensors under obligations of confidentiality which are no less strict than the confidentiality obligations imposed upon GSK hereunder. Regulus 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.

5.1.5 *Retained Rights*. All rights in and to GSK Technology and GSK's rights in Collaboration Technology not expressly licensed to Regulus hereunder, and any other Patent Rights or Know-How of GSK or its Affiliates, are hereby retained by GSK or such Affiliate.

5.2 License Grants to GSK.

5.2.1 *Development and Commercialization License*. On a Program-by-Program basis, subject to the terms and conditions of this Agreement (including without limitation Section 12.7.3(d)) and the Third Party and Parent-Originated Rights and Obligations, solely upon GSK's exercise of any of its Program Options in accordance with the provisions of Article 4 or by operation of the applicable termination provisions of Article 12 wherein the effect of such termination is the grant of an exclusive license to GSK under this Section 5.2, and solely with respect to the Collaboration Compounds, Option Compounds and Licensed Products under the Program for which GSK exercises its Program Option or to which such Program termination under Article 12 applies, Regulus hereby grants to GSK, effective as of the date of such exercise of the relevant Program Option (except to the extent set forth in Section 12.7.3(d)) or the date of operation of such provision under Article 12, a worldwide, exclusive, royalty-bearing (only in accordance with Section 6.6.1 and Section 6.6.2 and subject to Sections 12.7.3(a), 12.7.3(b), 12.7.3(c), 12.7.5 and 12.7.7(d)), sublicenseable (in accordance with Section 5.2.2 below) license in the Field, under the Regulus Technology and Regulus' rights under any Collaboration Technology,

(a) to Develop miRNA Compounds and miRNA Therapeutics,

(b) to Manufacture miRNA Compounds and miRNA Therapeutics, and

(c) to Commercialize miRNA Compounds and miRNA Therapeutics.

5.2.2 *Sublicense Rights*. Subject to Third Party and Parent-Originated Rights and Obligations and to the terms and conditions of this Agreement (including without limitation Section 12.7.3(d)), GSK shall have the right to grant to its Affiliates and/or Third Parties sublicenses under the licenses granted under Section 5.2.1 above; provided, that, each such sublicense shall be subject and subordinate to, and consistent with, the applicable terms and conditions of this Agreement. [***]; provided, that for Agreements that are entered into by GSK or its Affiliates after the Effective Date, where GSK has or can readily [***] 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.

5.2.3 *Trademarks for Licensed Products*. If GSK has exercised its Program Option with respect to a Program hereunder, to the extent that Regulus owns any trademark(s) which were used prior to the exercise of the Program Option by GSK that are specific to any Option Compound Developed under such Program and GSK reasonably believes such trademark(s) would be reasonably necessary or useful for the marketing and sale in the Field in the Territory of such Option Compound or related Licensed Products, Regulus shall, upon GSK's request [***], assign its rights and title to such trademark(s) to GSK reasonably in advance of the First Commercial Sale of such Licensed Products. Other than the trademarks described above which are owned by Regulus prior to the exercise of a Program Option by GSK, the Commercializing Party shall be solely responsible for developing, selecting, searching, registration and maintenance of, and shall be the exclusive owner of all trademark(s), trade dress, logos, slogans, designs, copyrights and domain names used on and/or in connection with any of the Option Compounds and Licensed Products resulting from a Program.

5.2.4 *Retained Rights*. 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 [***] 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 [***] in the Isis Field (each as defined in the Regulus License Agreement). All rights in and to Regulus Technology and Regulus' rights in Collaboration Technology 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 Regulus or its Parent Companies or Affiliates, are hereby retained by Regulus or such Parent Company or Affiliate.

5.3 Technology Transfer after Exercise by GSK of a Program Option.

5.3.1 *Generally*. After GSK exercises its Program Option for a Program hereunder, and during a period not to exceed [***] thereafter, Regulus shall promptly deliver to GSK, at no cost to GSK (except as set forth in Section 5.3.2 below), all Regulus Technology and Regulus Collaboration Technology in Regulus' possession or Control relating to the Option Compounds Developed under such 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 5.2.1, (b) pre-clinical and clinical data and results (including pharmacology, toxicology, emulation and stability studies), adverse event data, protocol results, analytical methodologies, (c) copies of patent applications and patents included within Regulus Patents and Regulus Collaboration Patents and other relevant patent information, (d) regulatory filings (including all relevant INDs and Regulatory Approvals), regulatory documentation, regulatory correspondence, and applicable reference standards; and (e) 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 Option Compounds, as further described in and subject to Section 5.3.2 below. All information should be supplied to GSK in electronic format to the extent possible. Without limiting the foregoing, Regulus shall use Diligent Efforts to perform the transfer of such information and materials to GSK in an orderly manner and without undue interruption of GSK's Development of Option Compounds and related Licensed Products hereunder, and, upon delivery of such information and materials to GSK, GSK shall use Diligent Efforts to promptly implement such information and materials into its Development and Commercialization activities with respect to such Option Compounds and related Licensed Products hereunder. For the avoidance of doubt, the obligation on Regulus to deliver to GSK all Regulus Technology and other Know-How and information in accordance with this Section 5.3.1 shall include (i) the procurement of any Regulus Technology in the possession of any Regulus Affiliate or Parent Company engaged by Regulus as a subcontractor in accordance with Section 3.10 and (ii) the use of Diligent Efforts to procure any Regulus Technology in the possession of any Third Party subcontractor engaged by Regulus as a subcontractor in accordance with Section 3.10.

5.3.2 *Certain Regulus Responsibilities*. After exercise by GSK of a Program Option, within the [***] month period set forth in Section 5.3.1, Regulus shall use its Diligent Efforts to:

(a) transfer to GSK, at no cost to GSK, ownership of all relevant regulatory filings relating to the applicable Option Compounds, including all INDs, to the extent permitted under applicable law; provided, that, at GSK's reasonable discretion if no such transfer is reasonably practical, then Regulus shall grant to GSK a right of reference to such regulatory filings; and

(b) at GSK's request, transfer to GSK or its designee, subject to the payment [***] then existing supplies, which are deemed suitable by GSK, of such Option Compounds, including Back-up Compounds and other Collaboration Compounds under such

Program, and the Parties will use good faith efforts to work together to have any Third Party manufacturing arrangements solely covering the Manufacture of such Option Compounds assigned to GSK (it being understood that no such assignment shall be required if such assignment is conditional upon [***]). If such bulk drug substance or other materials are not in Regulus' possession and Control or are not reasonably transferable, Regulus shall provide notice to GSK and, upon reasonable request by GSK, use good faith efforts to assist GSK in obtaining access to such materials.

5.3.3 *Continuing Cooperation*. For a [***] month period and thereafter for such time as is reasonably requested by GSK acting in good faith to transfer and reproduce the Manufacturing process for the Option Compounds after the transfer described in Section 5.3.1 and 5.3.2 above, Regulus shall use reasonable efforts, which shall not exceed the equivalent of [***] (unless mutually agreed by the Parties where reasonably necessary), to cooperate fully with GSK to conduct any additional transfer of the Manufacturing process for the Option Compounds to GSK or to a Third Party as nominated by GSK and to provide GSK with any other Regulus Technology or Regulus Collaboration Technology, as it may be developed or identified to which GSK has a right or license under this Agreement that is necessary or useful for GSK to further Develop, Manufacture, Commercialize or otherwise exploit the progression of Collaboration Compounds into Licensed Product(s) as permitted under this Agreement.

5.3.4 *Additional Services*. In the event that GSK reasonably requests Regulus to provide GSK with any materials or services beyond those set forth in Sections 5.3.1, 5.3.2, and 5.3.3, such materials and/or services may be scheduled and provided by Regulus 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.

ARTICLE 6

MILESTONES AND ROYALTIES; PAYMENTS

6.1 Upfront Payment to Regulus. In partial consideration for GSK's Program Options hereunder, 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 Fifteen Million U.S. Dollars ($15,000,000) no later than [***] Business Days after receipt by GSK of an invoice sent from Regulus on or after the Effective Date of this Agreement (the **"Upfront Payment"**).

6.2 Purchase of Regulus Promissory Note. GSK agrees to lend Regulus Five Million Dollars ($5,000,000). The loan shall be evidenced by a convertible promissory note, in the form

of the Convertible Promissory Note, attached hereto as Exhibit H. Within [***] Business Days of the date on or after the Effective Date that GSK receives an invoice from Regulus therefor, (a) GSK shall pay Regulus Five Million Dollars ($5,000,000) by wire transfer of immediately available funds to an account designated by Regulus in writing and (b) Regulus shall deliver to GSK the Convertible Promissory Note in the amount of Five Million Dollars ($5,000,000).

6.3 Program Option Exercise Fees. Upon the exercise by GSK of its Program Option for a given Program in accordance with the provisions of Section 4.2, GSK shall pay to Regulus the applicable Program Option Exercise Fee as shown in the table in Section 6.4 within [***] days of receipt by GSK of an invoice sent from Regulus on or after the date that Regulus receives written notice from GSK of GSK's decision to exercise its Program Option.

6.4 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 6.4 after written notice of the achievement by or on behalf of Regulus or GSK (as applicable) is provided to the other Party of each of the listed events (each, a "**Milestone Event**") and within [***] days of receipt by GSK of an invoice sent from Regulus on or after the date of achievement of such Milestone Event. GSK shall send Regulus a written notice thereof promptly following the date of achievement of each Milestone Event by or on behalf of GSK.

Milestone Event	GSK exercises its Program Option at [***] Stage ("Table 1 Rates") US$Million ("m")	("Table 2 Rates") US$Million ("m")	GSK exercises its Program Option at [***] ("Table 3 Rates") US$Million ("m")
Development Milestone Events:			
[***]*	[***]	[***]	[***]
Reaching [***]*	[***]	[***]	[***]
[***]**	[***]	[***]	[***]
[***]**	[***]	[***]	[***]
[***]***	[***]	[***]	—
[***]	—	—	[***]
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]
[***] Milestone Events:			
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]
TOTAL Potential Milestones	[***]	[***]	[***]

*These milestones are payable upon achievement of the event, regardless of whether [***] or not.

The [***] Milestone Event shall occur upon [***] that the Discovery Milestone has been met.

**For each of these milestones, GSK pays the Table 1 Rate or Table 2 Rate, as applicable, if GSK achieves the Milestone Event (i.e., if GSK had exercised its Program Option at [***] Stage or otherwise prior to [***]) or the Table 3 Rate if Regulus achieves the Milestone Event (i.e., if GSK had not so exercised its Program Option but Regulus continued developing the Collaboration Compound).

***This milestone is only payable where GSK exercises the Program Option prior to [***]. This Milestone Event will be met as determined by GSK; provided, however, that the Milestone Event will be deemed to have been met if, after conducting a [***], GSK moves the relevant Program forward through clinical development by Initiating either a [***] with respect to such Program. In addition, if GSK has not [***] but has not terminated the Program and returned the Collaboration Compounds under such Program to Regulus as Returned Licensed Products, then this Milestone Event will be deemed to have been met.

6.5 Limitations on Milestone Payments

6.5.1 No milestone payments are owed for any Milestone Event that is not achieved and in the case where one Option Compound or Licensed Product is substituted for another, then the milestones payable with respect to the new Option Compound or Licensed Product are only for future Milestone Events.

6.5.2 Each milestone will be paid only once per Program upon the first achievement of the Milestone Event, regardless of the number of Option Compounds or Licensed Products resulting under the Program, and regardless of whether any such Option Compound or Licensed Product constitutes a [***] product or any combination of the foregoing. The Discovery Milestone will be paid a maximum of [***] times, once for each of the [***] Programs, upon the first achievement of such Milestone Event for each Program, and will not be paid again for the Initial Collaboration Targets in the event that either or both such Initial Collaboration Targets are substituted with other Targets pursuant to Section 3.2.

6.5.3 Notwithstanding any of the foregoing, upon GSK's exercise of a Terminated Program Option pursuant to Section 4.2.3:

(a) before the achievement of the [***], GSK shall pay Regulus milestones at [***] of the [***] set forth above;

(b) after the achievement of the [***] but prior to the [***] for such Program, then GSK shall pay Regulus milestones at [***] set forth above; and

(c) after [***] for such Program, but prior to the [***], then GSK shall pay Regulus milestones at [***] set forth above.

6.5.4 If GSK exercises its Program Option after [***] by the Leading Compound under the Program but GSK immediately substitutes such Leading Compound by a Back-up Compound under such Program in accordance with Section 4.2.4, then GSK shall pay Regulus milestones at the [***] set forth above, except as set forth in Section 4.2.4.

6.5.5 Upon GSK's exercise of a Program Option pursuant to Section 4.2.5:

(a) before the achievement of [***], GSK shall pay Regulus milestones at the [***] set forth above;

(b) after the achievement of [***] but prior to the [***] for such Program, then GSK shall pay Regulus milestones at the [***] Rates set forth above; and

(c) after [***] for such Program, but prior to the [***], then GSK shall pay Regulus milestones at the [***] set forth above.

6.5.6 For purposes of clarity, milestones shall be payable by GSK to Regulus under Section 6.4, subject to Section 6.5 and Article 12, with respect to the achievement of any Milestone Event set forth in Section 6.4 by a Collaboration Compound for [***] in the Field, to the same extent as would be payable with respect to the achievement of such Milestone Event by a Collaboration Compound or Licensed Product for [***] Indication hereunder. With respect to any Collaboration Compound or Licensed Product for use as an [***] product in the Field, the Parties shall negotiate in good faith the [***] upon achievement of which milestone payments would be payable with respect to such [***] product.

6.6 Royalty Payments to Regulus.

6.6.1 *GSK Patent Royalty*. As partial consideration for the rights granted to GSK hereunder, GSK will pay to Regulus royalties on Annual Net Sales of the Royalty-Bearing Products sold by GSK, its Affiliates or Sublicensees during a calendar year, on a country-by-country basis and Royalty-Bearing Product-by-Royalty-Bearing Product basis, in the countries of the Territory in which there is a Valid Claim within the Regulus Technology or Collaboration Technology (excluding GSK Collaboration Technology [***] of the Licensed Product being

sold, in the amounts as follow (the "**GSK Patent Royalty**"). For purposes of clarity, royalties shall be payable by GSK to Regulus under this Section 6.6.1, subject to Section 6.6.2, 6.8 and Article 12, with respect to sales of a Collaboration Compound or Licensed Product that has obtained Regulatory Approval as [***] to the same extent as would be payable with respect to Net Sales of a Licensed Product that has obtained Regulatory Approval for the treatment of [***] Indication hereunder, provided, that, in no event shall GSK be obligated to pay royalties more than once with respect to the same unit of such Collaboration Compound or Licensed Product, as applicable.

(a) Subject to the provisions of Sections 6.6.1, 6.6.2 and 6.8, GSK shall pay to Regulus the royalties at the percentages as described in the table below:

Annual Net Sales (U.S. $ Million) of Licensed Products per Program per calendar year US$Million ("m")	**GSK exercises its Program Option at [***] Stage "Table 1 Rates"**	**"Table 2 Rates"**	**GSK exercises its Program Option at [***] "Table 3 Rates"**

Up to $[***]m	[***]	[***]	[***]
>[***] up to [***]	[***]	[***]	[***]
>[***] up to [***]	[***]	[***]	[***]
> [***]	[***]	[***]	[***]

(b) In the event any Combination Product(s) are sold, royalties on such Combination Products will be determined pursuant to Section 1.113.

(c) The royalty rates in the table above are incremental rates, which apply only for the respective increment of Annual Net Sales described in the Annual Net Sales column. Thus, once a total Annual Net Sales figure is achieved for the year, the royalties owed on any lower tier portion of Annual Net Sales are not adjusted up to the higher tier rate.

(d) Notwithstanding any of the foregoing, upon GSK's exercise of a Terminated Program Option pursuant to Section 4.2.3:

(i) before the achievement of [***], GSK shall pay Regulus royalties at [***] of the [***] set forth above;

(ii) after the achievement of [***], but prior to the [***] for such Program, then GSK shall pay Regulus royalties at the [***] set forth above; and

(iii) after [***] for such Program, but prior to the [***], then GSK shall pay Regulus royalties at the Table 2 Rates set forth above.

(e) If GSK exercises its Program Option after [***] by the Leading Compound under the Program but GSK immediately substitutes such Leading Compound by a Back-up Compound under such Program in accordance with Section 4.2.4, then GSK shall pay Regulus royalties at the [***] set forth above, except as set forth in Section 4.2.4.

(f) Upon GSK's exercise of a Program Option pursuant to Section 4.2.5:

(i) before the achievement of the [***], GSK shall pay Regulus royalties at the [***] set forth above;

(ii) after the achievement of the [***] but prior to the [***] for such Program, then GSK shall pay Regulus royalties at the [***] set forth above; and

(iii) after [***] for such Program, but prior to the [***], then GSK shall pay Regulus royalties at the [***] set forth above.

6.6.2 Application of Royalty Rates. All royalties set forth under Section 6.6 shall always be subject to the provisions of this Section 6.6.2, and shall only 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 or Combination Product until the date of [***] within the [***] of the Licensed Product; provided, however, that with respect to those cases where (i) the only Valid Claim is [***], or (ii) the only Valid Claim within the [***] of the Licensed Product or (B) a claim that covers the [***] of a miRNA Compound or a miRNA Therapeutic) (such claim in clauses (i) or (ii) **[***]** of a Licensed Product or Combination Product, the rates with respect to such Licensed Product or Combination Product shall be reduced by [***] of the applicable rates specified in Section 6.6.1.

(b) *Pending Patents:* If, on a country-by-country and Licensed Product-by-Licensed Product basis, there is, at any time during the period within [***] years after the date of First Commercial Sale of such Licensed Product in such country, no Valid

Claim as described in paragraph (a) within the [***] in each case which covers the Licensed Product, but there is a pending patent application within the [***]in each case with a claim which covers the[***] of the Licensed Product which has been pending for more [***] years but for less than [***] years from the filing date of such patent application (a "**Pending Claim**"), then, during such time, not to extend beyond [***] years from the date of [***] of such Licensed Product in the relevant country, GSK will pay [***] of the otherwise applicable GSK Patent Royalty rates set forth in Section 6.6.1. In addition, where the only Pending Claim covering the Licensed Product would, if issued, be a [***], then the rates shall be reduced to be [***] of the otherwise applicable GSK Patent Royalty rates set forth in Section 6.6.1. Notwithstanding any of the foregoing, if the Pending Claim [***], then the applicable royalty rate will be, going forward from the time that such [***] and not retroactively, and GSK shall pay Regulus, [***] Royalty rates as set forth in the table in Section 6.6.1 above (subject to the [***] reduction if such Valid Claim qualifying under Section 1.196(a) resulting from the Pending Claim is a [***]) and for the duration stated under the "Patent Royalty Term" paragraph (a) above, but if the Pending Claim does not issue within [***] years of the date of filing of such patent application, then thereafter, GSK will no longer pay any royalty to Regulus with respect to such Pending Claim under this paragraph (b).

(c) *Know-How Royalty*: If, on a country-by-country and Licensed Product-by-Licensed Product basis, (i) at any time during the period within [***] years after the date of First Commercial Sale of such Licensed Product in such country, the only Valid Claims or Pending Claims within the [***]in each case which cover the [***] of the Licensed Product, are claims that cover [***] a miRNA Compound or a miRNA Therapeutic, or (ii) there [***], at any time during the period within [***] years after the date of First Commercial Sale of such Licensed Product in such country, Valid Claims or Pending Claims within the [***]in each case which covered the[***] of the Licensed Product, but such Valid Claims and Pending Claims [***], then, during

such time described in clauses (i) or (ii), not to extend beyond [***] years from the date of First Commercial Sale of such Licensed Product in such country, GSK will pay Regulus a royalty at the rate of [***] of the GSK Patent Royalty rates as described in Section 6.6.1 above. For example, but not limitation, if at the time of First Commercial Sale of a Licensed Product in a given country Regulus has a Valid Claim described in paragraph (a) above that has been pending for [***] years, then for the first [***] years after such First Commercial Sale the royalty rate shall be determined under paragraph (a) above and, if such claim does not issue within such [***] year period, then for a period of [***] years the royalty rate shall be determined under paragraph (b) above, and for the remaining [***] years after such First Commercial Sale, the royalty rate shall be determined under this paragraph (c). In no event shall

the royalty described in this paragraph (c) be paid for more than [***] years after First Commercial Sale of such Licensed Product in the relevant country, and in all cases the royalty shall be subject to paragraphs (d), (e) and (f) below. For the sake of clarity, the [***] year period described in this paragraph (c) shall not reduce the period during which royalties are payable pursuant to paragraphs (a) or (b) above, as applicable.

(d) *Reduction of Royalty for Competition from Generic Products*: If at any time during the Agreement Term any Generic Products enter the market for a Royalty-Bearing Product and during the applicable Calendar Quarter, on a country-by-country and Licensed Product-by-Licensed Product basis, such Generic Products taken in the aggregate have a market share (measured in scripts 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 (a) at least [***], up to and including [***], GSK's obligation to pay royalties to Regulus on sales of the relevant Royalty-Bearing Products in such market will be reduced on a country-by-country basis to the amount which is [***] of the otherwise applicable royalty rate under clauses (a) through (c) of this Section 6.6.2, and (b) greater than [***] GSK's obligation to pay royalties to Regulus on sales of the relevant Products in such market will be reduced on a country-by-country basis to the amount which is [***] of the otherwise applicable royalty rate under clauses (a) through (c) of this Section 6.6.2.

(e) For purposes of clarity, no royalty is payable by GSK, its Affiliates or Sublicensees to Regulus, its Affiliates, Sublicensees, successors, assigns or Parent Companies at all under this Section 6.6 with respect to a Royalty-Bearing Product in a country, in the event that neither subsection (a), (b) nor (c) above applies at the time of sale and in the country of sale for such Royalty-Bearing Product.

(f) *Limitation on Aggregate Reduction for GSK Royalties.* Notwithstanding anything in this Agreement to the contrary, on a Program-by-Program basis, in no event will Regulus receive royalties for Annual Net Sales of Licensed Products by GSK or its Affiliate or Sublicensee, with respect to any Calendar Quarter, less than the sum of [***], except where there has been an uncured material breach of the Agreement by Regulus, in which case, the royalty that Regulus will receive shall not be less than the sum of [***], and in any case under this subsection (f), the period for which payment of such [***] is required shall end when the royalty payment term would have ended under subsection (a), (b) or (c) above, as applicable.

6.7 Refused Candidate Products, Returned Licensed Products and Reverse Royalty Payments to GSK.

6.7.1 *Reverse Royalty*. In the event that Regulus or any of its Parent Companies or any of its or their Affiliates or Third Party licensees or Sublicensees Develops and Commercializes any Refused Candidate as a Refused Candidate Product, or any Returned Licensed Product, it shall pay the following royalty payments to GSK, following the First Commercial Sale by Regulus, its Affiliates or Sublicensees, on a country-by-country basis, for Annual Net Sales of all such products within the relevant Program (**"Reverse Royalties"**) as follows:

(I) Upon Termination [***] of a Program due to [***]	**Reverse Royalty Rate (paid to GSK) US$Million ("m")**
(A) For Refused Candidate Products with respect to such Program, if [***] occurs prior to [***]	[***]
(B) For Returned Licensed Products with respect to such Program, if [***] occurs after [***]	[***]
(II) Upon [***] Termination [***] of a Program [***]	**Reverse Royalty Rate (paid to GSK)**
(A) For Refused Candidate Products with respect to such Program, if [***] occurs [***]	[***]
(B) For Refused Candidate Products with respect to such Program, if [***] occurs [***]	[***]
(C) For Returned Licensed Products with respect to such Program, if [***] occurs after [***], but before [***].	[***]
(D) For Returned Licensed Products with respect to such Program, if [***] occurs after [***] and after [***].	[***]

6.7.2 *Commercialization by Regulus' Affiliates and Sublicensees*. Regulus' obligation to pay the Reverse Royalty to GSK above on Net Sales of Refused Candidate Products or Returned Licensed Products will apply regardless of whether such sales are made by Regulus or by any of its Affiliates, Parent Companies (to the extent that they are selling such Refused Candidate Product or Returned Licensed Product) or Sublicensees, and will

continue on a country-by-country and product-by-product basis for the Agreement Term. For purposes of clarity, royalties shall be payable by Regulus to GSK under this Section 6.7, subject to the remainder of this Section 6.7 and Article 12, with respect to sales of any Refused Candidate, Refused Candidate Product or Returned Licensed Product that has obtained Regulatory Approval [***] or for the treatment [***] Indication to the same extent as would be payable with respect to Net Sales of a Refused Candidate Product or Returned Licensed Product that has obtained Regulatory Approval for the treatment [***] Indication hereunder, provided, that, in no event shall Regulus be obligated to pay royalties more than once with respect to the same unit of such Refused Candidate, Refused Candidate Product or Returned Licensed Product, as applicable.

6.7.3 *Limitation on Reverse Royalties*. The Reverse Royalties payable under Section 6.7.1(I)(B), (II)(B) and (II)(C) above with respect to any Refused Candidate Product or Returned Licensed Product shall be payable by Regulus to GSK up to, and in no event in excess of, an amount equal to [***] which such Refused Candidate Product or Returned Licensed Product was subject [***], (b) any [***] activities conducted by Regulus under such Program, (c) any [***] with respect to Licensed Products arising from such Program and Commercialized by GSK [***], plus (d) any [***] attributable to such Program. Within [***] days after the date on which Regulus obtains rights to the Refused Candidate Product or Returned Licensed Product with respect to a Program pursuant to this Agreement, GSK shall provide to Regulus a written notice [***]. For purposes of clarity, the Reverse Royalties payable under Section 6.7.1(II)(D) above shall not be subject to the foregoing limitation.

6.8 Fundamental and Program Specific Intellectual Property.

6.8.1 *Fundamental IP*. Regulus will be solely responsible for paying its Total License Pass-Through Costs for any Regulus Technology (a) owned by Regulus or its Affiliates or any of the Parent Companies as of the Effective Date, (b) invented by any of the Parent Companies during the Agreement Term, or (c) [***] as of the Effective Date or during the Agreement Term as [***] for the use or exploitation of miRNA Antagonist technology generally as contemplated under the Program(s) during the Collaboration Term, and which is not [***] hereunder (the foregoing clauses (a), (b) and (c), collectively, the "**Fundamental IP**").

6.8.2 *Program-Specific Technology*. The Parties shall [***] all [***] incurred after the Effective Date and included within [***] for any [***] as of the Effective Date or during the Agreement Term to the extent such [***] (a) pertains [***], or (b) relates to [***] (clauses (a) and (b), collectively, the "**Program-Specific Technology**"; provided, however, that any of the same under clauses (a) or (b) would instead be Fundamental IP if the terms and conditions of Section 6.8.1 are met for any such intellectual property), which GSK agrees (such agreement not to be unreasonably withheld, conditioned or delayed) is [***] under a Program hereunder. By way of illustration but not limitation, the Parties agree that the [***] Controlled by Regulus as of the Effective Date (which Patent Rights are set forth on [***]) will be deemed Program-Specific Technology. Any [***] described herein which apply to a Program(s) as well as other activities shall be reasonably allocated to the relevant Program. Notwithstanding the foregoing, Regulus will be [***] for paying all [***] owed to the relevant Third Party licensors pursuant to the [***]. GSK [***] of such amounts within [***] days after GSK's [***] from Regulus therefor.

6.8.3 *Reduction by GSK for Third Party Licenses.* If GSK reasonably determines that it needs to obtain one or more licenses from one or more Third Parties (other than any license described in the paragraphs in this Section 6.8 above) to Develop, Manufacture or Commercialize any Option Compound or related Licensed Product, GSK may obtain such license [***] (a) [***] of such license reasonably in advance of entering into such license, to enable [***] on such license terms, and (b) considering in good faith [***] with respect thereto. GSK may then obtain such license, which shall be deemed included in GSK Technology hereunder, and may offset [***] of GSK's Third Party License Pass-Through Costs associated with acquiring such Third Party license(s) against any [***] due to Regulus; provided, that in no event will Regulus receive, with respect to any Calendar Quarter, less than [***]. GSK shall have the right to carry forward and apply in future Calendar Quarters or years any such unused offset to which GSK is entitled in the event that such [***] would be exceeded, until [***] of offset or deduction to which GSK is entitled is fully satisfied. Notwithstanding any of the foregoing, GSK may, without having to comply with clause (a) or (b) above, unilaterally decide to include as GSK Technology any Third Party license(s) for [***], provided, however, that GSK shall not have the right to offset against any [***] due to Regulus hereunder any Third Party License Pass-Through Costs associated with acquiring any such Third Party license(s) (it being understood that if Regulus agrees in advance, as set forth in the first sentence of this Section 6.8.3, that GSK should obtain such Third Party license(s) for [***] and implement such intellectual property rights into GSK's Development, Manufacture and/or Commercialization activities with respect to Option Compounds or related Licensed Products hereunder, then GSK

shall have the right to offset against [***] due to Regulus any such Third Party License Pass-Through Costs).

6.9 Payments.

6.9.1 *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 shall be made by the Commercializing Party to the other Party under this Agreement within [***] days following the end of each such Calendar Quarter. Each royalty payment shall 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, the Payor shall submit a royalty report so indicating.

6.9.2 *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 Licensed Products sold in a currency other than U.S. dollars, such currency shall be converted into U.S. dollars as calculated at the [***] for the pertinent quarter or year to date, as the case may be, as used by the Payor in producing its quarterly and annual accounts. Such payments shall be without deduction of exchange, collection or other charges.

6.9.3 *Records Retention*. Commencing with the First Commercial Sale of a Licensed Product, the Payor shall keep complete and accurate records pertaining to the sale of such Licensed Products, for a period of [***] 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.

6.10 Audits. During the term of this Agreement and for a period of [***] 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 [***] made under this Agreement for any period within the preceding [***] years. The independent, certified public accountant shall disclose to the Payee only the royalty and, if applicable, [***] 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. Regulus shall also have the right to have audited, in accordance with this Section 6.10, the relevant books and records of GSK as may be necessary for the sole purpose of verifying the

amount of (a) [***] GSK shall also have the right to have audited, in accordance with this Section 6.10, the relevant books and records of [***] 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 [***] or (except for the information expressly sought to be confirmed by the auditing Party as set forth in this Section 6.10) 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 or, if applicable, milestone amount which should have been paid, then such audited Party shall make all payments required to be made, or (y) the amount paid to [***] 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 [***] 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 and, if applicable, [***] made by the audited Party were less than [***] 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.

6.11 Taxes.

6.11.1 *Sales or Other Transfers*. The recipient of any transfer under this Agreement of Regulus Technology, GSK Technology, Confidential Information, Collaboration Compounds, Licensed Products (including Returned Licensed Products), as the case may be, shall be solely responsible for any sales, use, value added, excise or other taxes applicable to such transfer.

6.11.2 *Withholding Tax*. The Parties acknowledge and agree that, under applicable laws in effect as of the Effective Date, [***] from [***] under this Agreement. Consequently, GSK agrees [***]. 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 upfront payment) 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 limited liability company 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 [***]. Regulus shall notify GSK immediately in writing in the event that Regulus ceases to be [***]. Pending receipt of formal certification from the UK Inland Revenue, GSK may pay royalty income and any other payments (other than the upfront payment) 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 other similar body alleging that GSK was [***], except that Regulus' indemnification obligation under this Section 6.11.2 shall not apply to GSK's payment of the [***]. GSK shall indemnify and hold harmless Regulus and its Parent Companies against any loss, damage, expense or liability arising in any way from a claim [***].

ARTICLE 7

EXCLUSIVITY

7.1 Exclusivity Binding on Both Parties. Except as set forth in Section 7.3 below or in Article 12, during the Agreement Term, neither Party nor its Affiliates, nor any of Regulus' Parent Companies, will work with (or for the benefit of or grant any license to) any Third Party or independently outside this Agreement to [***] that is [***] any Collaboration Target hereunder.

7.2 Additional Regulus Exclusivity Obligations. Except as set forth in Section 7.3 below or in Article 12, during the Research Collaboration Term for each Program, neither Regulus nor its Affiliates will work with (or for the benefit of or grant any license to) any Third Party or independently outside of this Agreement to [***] any [***] any Collaboration Target hereunder.

7.3 Exclusions.

7.3.1 *[***]* For purposes of clarity, the foregoing covenants in Sections 7.1 and 7.2 shall not apply to either Party, each Party's Affiliates or Regulus' Parent Companies with respect to any [***] in accordance with the provisions of Section [***].

7.3.2 *Refused Candidates; Refused Candidate Products; Returned Licensed Products*. In addition, in no event shall the covenants in Sections 7.1 and 7.2 apply to bind or restrict Regulus, its Affiliates or Parent Companies with respect to any Blocked Target, Refused Candidate, Refused Candidate Product or Returned Licensed Product.

7.3.3 *Permitted Uses by Parent Companies*. Notwithstanding any of the foregoing, (a) each Parent Company shall have the right to grant Permitted Licenses as contemplated under the Regulus License Agreement and as defined herein (it being understood

that the exception set forth in this clause (a) to the Parent Company's exclusivity obligations under Section 7.1 shall not apply with respect to a right granted to a Third Party if such right does not satisfy the definition of "Permitted License" under this Agreement at the time in question), (b) Alnylam shall have the right to perform its own internal Research in the Alnylam Field (each as defined in the Regulus License Agreement), and (c) Isis shall have the right to perform its own internal Research in the Isis Field (as defined in the Regulus License Agreement).

ARTICLE 8

OWNERSHIP OF INTELLECTUAL PROPERTY AND PATENT PROSECUTION

8.1 Ownership.

8.1.1 *Regulus Technology and GSK Technology*. As between the Parties, Regulus shall own and retain all of its rights, title and interest in and to the Regulus Know-How and Regulus Patents and GSK shall 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.

8.1.2 *Collaboration Technology*. As between the Parties, GSK shall be the sole owner of any Collaboration Know-How discovered, developed, invented or created solely by or on behalf of GSK and/or its Affiliates ("**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 shall retain all of its rights, title and interest thereto, subject to any rights or licenses expressly granted by GSK to Regulus under this Agreement. As between the Parties, Regulus shall be the sole owner of any Collaboration Know-How discovered, developed, invented or created solely by or on behalf of Regulus and/or its Affiliates ("**Regulus Collaboration Know-How**") and any Patent Rights that claim or cover Regulus Collaboration Know-How ("**Regulus Collaboration Patents**" and, together with the Regulus Collaboration Know-How, the "**Regulus Collaboration Technology**"), and shall retain all of its rights, title and interest thereto, subject to any rights or licenses expressly granted by Regulus to GSK under this Agreement. Any Collaboration Know-How that is discovered, developed, invented or created jointly 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**"), shall be owned jointly by GSK and Regulus 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 shall 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 shall promptly disclose to the other Party in writing, and shall cause its Affiliates to so disclose, the discovery, development, invention or creation of any Jointly-Owned Collaboration Technology.

8.1.3 *Determining Inventorship*. The determination of inventorship shall be made in accordance with United States patent laws. The Joint Patent Subcommittee shall discuss all matters pertaining to the determination of inventorship and, in case of a dispute in the Joint Patent Subcommittee (or otherwise between Regulus and GSK) over inventorship and, as a result, whether (i) any particular Collaboration Technology is solely owned by one Party or the other or jointly owned by both Parties or (ii) whether any particular Know-How is Regulus Know-How, GSK Know-How or Collaboration Know-How, such dispute shall be resolved by independent patent counsel not 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 shall be binding on the Parties with respect to the issue of inventorship. Expenses of such patent counsel shall be shared equally by the Parties.

8.2 Prosecution and Maintenance of Patents.

8.2.1 *Patent Filings*. The Party responsible for Prosecution and Maintenance of any Collaboration Patents as set forth in Sections 8.2.2 and 8.2.3 shall use Diligent Efforts to obtain patent protection for Collaboration Compounds and Licensed Products, if and as applicable, using counsel of its own choice but reasonably acceptable to the other Party (provided, that GSK acknowledges and agrees that it has been advised of Regulus' patent counsel as of the Effective Date and that such patent counsel is reasonably acceptable to GSK), in the Major Countries and such other countries as the responsible Party shall see fit. If subsequent to the Effective Date, GSK determines that such patent counsel is not satisfactory, GSK will raise such concerns with the Joint Patent Subcommittee and GSK may request that such patent counsel be changed, such request shall not be unreasonably refused by Regulus.

8.2.2 *Regulus Patents and GSK Patents*.

(a) Regulus shall control and be responsible for all aspects of the Prosecution and Maintenance of all Regulus Patents and all Regulus Collaboration Patents, subject to Section 8.2.4.

(b) GSK shall control and be responsible for all aspects of the Prosecution and Maintenance of all GSK Patents and all GSK Collaboration Patents, subject to Section 8.2.4.

8.2.3 *Jointly-Owned Collaboration Patents*. The strategy for Prosecution and Maintenance of all Jointly-Owned Collaboration Patents shall be discussed by GSK and Regulus through the Joint Patent Subcommittee. Subject to Section 8.2.4, GSK shall have the first right to control and be responsible for the Prosecution and Maintenance of all Jointly-Owned Collaboration Patents, unless Regulus has obtained the licenses under Sections 5.1.2 or 5.1.3 with respect to the Program to which such Jointly-Owned Collaboration Patent primarily relates, in which event Regulus shall have the first right to control and be responsible for the Prosecution and Maintenance of such Jointly-Owned Collaboration Patents.

8.2.4 *Other Matters Pertaining to Prosecution and Maintenance of Patents*.

(a) Subject to Third Party and Parent-Originated Rights and Obligations, each Party shall keep the other Party informed through the Joint Patent Subcommittee as to material developments with respect to the Prosecution and Maintenance of such Collaboration Patents, Regulus Patents or GSK Patents for which such Party has responsibility for Prosecution and Maintenance pursuant to Sections 8.2.2, 8.2.3 or this Section 8.2.4, 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 Patent or any Collaboration 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 Patent or Collaboration Patent primarily relates to any Refused Candidate, Refused Candidate Product or Returned Licensed Product, GSK shall notify Regulus of such intention at least [***] days prior to the date upon which such Patent Right shall lapse or

become abandoned, and Regulus shall thereupon have the right, but not the obligation, to assume responsibility for the Prosecution and Maintenance thereof at its own expense (subject to Section 8.3.1) with counsel of its own choice.

(c) If, during the Agreement Term, Regulus intends to allow any Regulus Patent or any Collaboration Patent with respect to which Regulus is responsible for Prosecution and Maintenance to lapse or become abandoned without having first filed a continuation or substitution, then, if GSK has exercised, or has not yet exercised but retains the right to exercise, its Program Option with respect to the Program to which such Regulus Patent or Collaboration Patent primarily relates (other than any Refused Candidate, Refused Candidate Product or Returned Licensed Product), Regulus shall notify GSK of such intention at least [***] days prior to the date upon which such Patent Right shall lapse or become abandoned, and GSK shall thereupon have the right, but not the obligation, to assume responsibility for the Prosecution and Maintenance thereof [***] (subject to Section 8.3.1) with counsel of its own choice.

(d) The Parties, through the Joint Patent Subcommittee, will cooperate in good faith to determine if and when any divisional applications shall be filed with respect to any Collaboration Patents or Regulus Patents, and where a divisional patent application filing would be practical and reasonable, then such a divisional filing shall be made and (i) GSK shall have the first right to control the Prosecution and Maintenance of such claims within Collaboration Patents or Regulus Patents which solely cover Collaboration Compounds with respect to a Program after exercise of a Program Option by GSK, or (ii) Regulus shall have the first right to control the Prosecution and Maintenance of such claims within Collaboration Patents or Regulus Patents which solely cover Refused Candidates, Refused Candidate Products or Returned Licensed Products. If the Party responsible for Prosecution and Maintenance pursuant to this Section 8.2.4(d) is an owner or co-owner of such Collaboration Patent or Regulus Patent, the other Party shall have the step-in right described in clauses 8.2.4(b) or (c), as applicable. If the Party responsible for Prosecution and Maintenance pursuant to this Section 8.2.4(d) is neither an owner nor co-owner of such Collaboration Patent or Regulus Patent and if such Party intends to allow such Collaboration Patent to lapse or become abandoned without having first filed a continuation or substitution, then such Party shall notify the other Party of such intention at least [***] days prior to the date upon which such Patent Right shall lapse or become abandoned, and such other Party shall thereupon have the right, but not the obligation, to assume responsibility for the Prosecution and Maintenance thereof [***] (subject to Section 8.3.1) with counsel of its own choice.

(e) In addition, the Parties shall consult, through the Joint Patent Subcommittee, 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 has an ownership interest, is licensed or sublicensed thereunder or may in the future, in accordance with this Agreement, obtain a license or sublicense thereunder.

8.3 Patent Costs.

8.3.1 *Jointly-Owned Collaboration Patents*. Regulus and GSK shall [***] 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 [***] for filing, prosecuting and maintaining any Jointly-Owned Collaboration Patents in a particular country or particular countries, in which case the declining Party shall, and shall 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.

8.3.2 *Regulus Patents and GSK Patents*. Except as set forth in Sections 8.2.4 and 8.3.1, each Party shall be responsible [***] incurred by such Party prior to and after the Effective Date in all countries in the Territory in the Prosecution and Maintenance of Patent Rights for which such Party is responsible under Section 8.2.

8.4 Defense of Claims Brought by Third Parties.

8.4.1 *Prior to Exercise of Program 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 Collaboration Compound (and related Licensed Products) being Developed under a Program with respect to which GSK has not yet exercised its Program Option (except for any Refused Candidate, Refused Candidate Product or Returned Licensed Product, which shall be subject to Section 8.4.3), Regulus shall have the first right, but not the obligation, to defend against such Proceeding at its sole cost and expense. In the event Regulus elects to defend against such Proceeding, Regulus shall have the sole right to direct the defense and to elect whether to settle such claim (but only with the prior written consent of GSK, not to be unreasonably withheld). In the event that Regulus elects not to defend against such Proceeding within [***] days after it first received written notice of the actual initiation of such Proceeding, GSK shall 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 Regulus with a written notice thereof within [***] days after

GSK's receipt of Regulus' notice of its election not to defend such Proceeding. After such exercise, GSK shall have the 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 Regulus, not to be unreasonably withheld). In any event, the Party not defending such Proceeding shall 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 directed by the other Party. Each Party shall 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 shall promptly furnish the other Party with a copy of each communication relating to the alleged infringement that is received by such Party. Notwithstanding any of the above, in the event that one of the Parent Companies brings a claim against GSK, GSK shall have the sole right to control the defense of any such claim at its sole cost.

8.4.2 *Following Exercise of Program 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 Collaboration Compound (and related Licensed Products) being Developed or Commercialized under a Program with respect to which GSK has exercised its Program Option (except for a Refused Candidate, Refused Candidate Product or Returned Licensed Product, which shall be subject to Section 8.4.3), GSK shall 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 shall have the sole right to direct the defense and to elect whether to settle such claim (but only with the prior written consent of Regulus, not to be unreasonably withheld). In the event that GSK elects not to defend against a particular proceeding, then it shall so notify Regulus in writing within [***] days after it first received written notice of the actual initiation of such Proceeding and, during such sixty-day period, shall take such reasonable measures as may be necessary to preserve Regulus' legal right to defend against such Proceeding. In such event, Regulus shall have the right, but not the obligation, to defend against such Proceeding at its sole cost and expense and thereafter shall 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 shall 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 directed by the other Party. Each Party shall 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 shall promptly furnish the other Party with a copy of each communication relating to the alleged infringement that is received by such Party.

8.4.3 *Refused Candidates, Refused Candidate Products and Returned Licensed 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 Refused Candidate, Refused Candidate Product or Returned Licensed Product, Regulus shall have the sole and exclusive right, but not the obligation, to defend against and settle such Proceeding at its sole cost and expense. In any event, GSK shall reasonably assist Regulus in defending such Proceeding and cooperate in any such litigation at the request and expense of Regulus. Each Party may at its own expense and with its own counsel join any defense directed by the other Party. GSK shall provide Regulus with prompt written notice of the commencement of any such Proceeding, or of any allegation of infringement of which GSK becomes aware, and shall promptly furnish Regulus with a copy of each communication relating to the alleged infringement that is received by GSK.

8.4.4 *Interplay between Enforcement of IP and Defense of Third Party Claims*. Notwithstanding the provisions of Section 8.4.1 through 8.4.3, to the extent that any action would involve the enforcement of the other Party's Know-How or Patent Rights, or the defense of an invalidity claim with respect to such other Party's Know-How or Patent Rights, the general concepts of Section 8.5 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 8.5, 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 8.5, to enforce such Know-How or Patent Rights or defend such invalidity claim).

8.5 Enforcement of Patents against Competitive Infringement.

8.5.1 *Duty to Notify of Competitive Infringement*. If either Party learns of an infringement, unauthorized use, misappropriation or threatened infringement by a Third Party with respect to any Regulus Collaboration Technology, Jointly-Owned Collaboration Technology, Regulus Technology or, solely for purposes of Section 8.5.4, GSK Technology or GSK Collaboration Technology, by reason of the Development, Manufacture, use or Commercialization 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 a miRNA Compound in any Collaboration Compound or Licensed Product (including Refused Candidates,

Refused Candidate Products or Returned Licensed Products, which are subject to Section 8.5.4) in the Field within the Territory ("**Competitive Infringement**"), such Party shall promptly notify the other Party and shall provide such other Party with available evidence of such Competitive Infringement.

8.5.2 *Prior to Exercise of Program Option*. For any Competitive Infringement with respect to a Collaboration Compound (and any related Licensed Product) (except for any Refused Candidate, Refused Candidate Product or Returned Licensed Product, which shall be subject to Section 8.5.4) that occurs after the Effective Date but prior to Program Option exercise in reference to the Program under which such Collaboration Compound is being Developed, Regulus shall have the first right, but not the obligation, to institute, prosecute, and control a Proceeding (including, without limitation, with respect to any defense or counterclaim brought in connection therewith that the Regulus Patents or Regulus Collaboration Patents are invalid or unenforceable), by counsel of its own choice, and GSK shall have the right to be represented in that action by counsel of its own choice at its own expense, however, Regulus shall have the right to control such litigation, irrespective of whether GSK is represented by counsel of its own choice. Notwithstanding the foregoing, GSK shall have the first right, but not the obligation, to institute, prosecute, and control a Proceeding (including, without limitation, with respect to any defense or counterclaim brought in connection therewith) in which the only claims are that Jointly-Owned Collaboration Patents are invalid or

unenforceable, by counsel of its own choice, and Regulus shall have the right to be represented in that action by counsel of its own choice at its own expense, however, GSK shall have the right to control such litigation, irrespective of whether Regulus is represented by counsel of its own choice. If Regulus fails to initiate a Proceeding (other than a Proceeding described in the second (2nd) sentence of this Section 8.5.2) within a period of [***] days after receipt of written notice from GSK or within a period of [***] days after the date Regulus first becomes aware of such Competitive Infringement (subject to a [***] day extension to conclude negotiations, if Regulus has commenced good faith negotiations with an alleged infringer for elimination of such Competitive Infringement within such [***] day period) and, within such [***] day or extended period, GSK has exercised its Program Option with respect to the relevant Program, then GSK shall have the right, but not the obligation, to initiate and control a Proceeding with respect to such Competitive Infringement by counsel of its own choice, and Regulus shall have the right to be represented in any such action by counsel of its own choice at its own expense. If GSK fails to initiate a Proceeding for Jointly-Owned Collaboration Patents, as provided in the second (2nd) sentence of this Section 8.5.2, within a period of [***] days after receipt of written notice from Regulus or within a period of [***] days after the date GSK first becomes aware of such Competitive Infringement (subject to a [***] day

extension to conclude negotiations, if GSK has commenced good faith negotiations with an alleged infringer for elimination of such Competitive Infringement within such [***] day period), then Regulus shall have the right, but not the obligation, to initiate and control a Proceeding with respect to such Competitive Infringement by counsel of its own choice, and GSK shall have the right to be represented in any such action by counsel of its own choice at its own expense.

8.5.3 *Following Exercise of Program Option*. For any Competitive Infringement with respect to any Option Compound (and any related Licensed Product) (except for any Refused Candidate, Refused Candidate Product or Returned Licensed Product, which shall be subject to Section 8.5.4) that occurs after GSK's exercise of a Program Option in reference to the Program under which such Option Compounds were Developed, GSK shall 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 the Regulus Patents, Regulus Collaboration Patents or Jointly-Owned Collaboration Patents are invalid or unenforceable) by counsel of its own choice at its own expense, and Regulus shall have the right, at its own expense, to be represented in that action by counsel of its own choice, however, GSK shall have the right to control such litigation, irrespective of whether Regulus is represented by counsel of its own choice. If GSK fails to initiate a Proceeding within a period of [***] days after receipt of written notice of such Competitive Infringement (subject to a [***] day extension to conclude negotiations, if GSK has commenced good faith negotiations with an alleged infringer for elimination of such Competitive Infringement within such [***] day period), Regulus shall have the right to initiate and control a Proceeding with respect to such Competitive Infringement by counsel of its own choice, and GSK shall have the right to be represented in any such action by counsel of its own choice at its own expense.

8.5.4 *Refused Candidates, Refused Candidate Products and Returned Licensed Products*.

(a) For any Competitive Infringement of any Regulus Technology, Regulus Collaboration Technology or Jointly-Owned Collaboration Technology with respect to a Refused Candidate, Refused Candidate Product or Returned Licensed Product, Regulus shall have the sole and exclusive 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 the Regulus Patents, Regulus Collaboration

Patents or Jointly-Owned Collaboration Patents are invalid or unenforceable), by counsel of its own choice at its own expense.

(b) For any Competitive Infringement of any GSK Technology or GSK Collaboration Technology with respect to a Refused Candidate, Refused Candidate Product or Returned Licensed Product, GSK shall 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 the GSK Technology or GSK Collaboration Technology are invalid or unenforceable), by counsel of its own choice at its own expense, and Regulus shall have the right to be represented in that action by counsel of its own choice at its own expense. If GSK fails to initiate a Proceeding within a period of [***] days after receipt of written notice of such Competitive Infringement (subject to a [***] day extension to conclude negotiations, if GSK has commenced good faith negotiations with an alleged infringer for elimination of such Competitive Infringement within such [***] day period) Regulus shall have the right, but not the obligation, to initiate and control a Proceeding by counsel of its own choice, and GSK shall have the right to be represented in any such action by counsel of its own choice at its own expense.

8.5.5 *Joinder.*

(a) If one Party initiates a Proceeding in accordance with this Section 8.5, 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 8.5.6, the costs and expenses of the Party initiating the Proceeding under this Section 8.5(a), and the costs and expenses of the other Party incurred pursuant to this Section 8.5.5(a), shall be borne by the Party initiating such Proceeding.

(b) If one Party initiates a Proceeding in accordance with this Section 8.5, 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.

8.5.6 *Share of Recoveries*. Any damages or other monetary awards recovered with respect to a Proceeding brought pursuant to this Section 8.5 shall be shared as follows: (i) the amount of such recovery shall first be applied to the Parties' reasonable out-of-pocket costs incurred in connection with such Proceeding (which amounts shall be allocated pro rata if insufficient to cover the totality of such expenses); and then (ii) any remaining proceeds shall be allocated between the Parties as follows: (A) if Regulus initiates the Proceeding pursuant to Sections 8.5.2, 8.5.3 or 8.5.4(a), [***]; (B) if GSK initiates the Proceeding pursuant to Sections 8.5.2 (except as described in the second (2nd) sentence thereof) or 8.5.4(b), [***]; (C) if GSK

initiates the Proceeding pursuant to Sections 8.5.2 (as described in the second (2nd) sentence thereof) or 8.5.3, [***], and [***] on such amount in accordance with [***]; and (D) if Regulus initiates the Proceeding pursuant to Section 8.5.4(b), such remaining proceeds [***], with [***] on such amount in accordance with [***]7 and [***] receiving the remainder.

8.5.7 *Settlement*. A settlement, consent judgment or other voluntary final disposition of a suit under this Section 8.5 may not be entered into without the consent of the Party not bringing the suit if such suit relates to those Patent Rights in which such Party not bringing the suit has an ownership interest, is licensed or sublicensed thereunder or may in the future, in accordance with this Agreement, obtain a license or sublicense thereunder.

8.5.8 *35 USC 271(e)(2) Infringement*. Notwithstanding anything to the contrary in this Section 8.5, for a Competitive Infringement under 35 USC 271(e)(2) the time periods set forth in Sections 8.5.2, 8.5.3 and 8.5.4(b) during which a Party shall have the initial right to bring a Proceeding shall 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 shall 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.

8.6 Other Infringement.

8.6.1 *Jointly-Owned Collaboration Patents*. With respect to the infringement of a Jointly-Owned Collaboration Patent which is not a Competitive Infringement, the Parties shall 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 8.6.1 shall be shared as follows: (i) the amount of such recovery shall first be applied to the Parties' reasonable out-of-pocket costs incurred in connection with such Proceeding (which amounts shall be allocated pro rata if insufficient to cover the totality of such expenses); and then (ii) (A) if the Parties jointly initiated a Proceeding pursuant to this Section 8.6.1, each Party shall retain or receive [***]; and (B) if only one Party initiates the Proceeding pursuant to Section 8.6.1, such Party shall [***].

8.6.2 *Patents Solely-Owned by Regulus*. Regulus shall retain all rights to pursue an infringement of any Patent Right solely owned by Regulus which is other than a Competitive Infringement and Regulus shall retain all recoveries with respect thereto.

8.6.3 *Patents Solely-Owned by GSK*. GSK shall retain all rights to pursue an infringement of any Patent Right solely owned by GSK which is other than a Competitive Infringement and GSK shall retain all recoveries with respect thereto.

8.7 Patent Listing.

8.7.1 *GSK's Obligations*. To the extent required or permitted by law, GSK will use Diligent Efforts to promptly, accurately and completely list, with the applicable Regulatory Authorities during the Agreement Term, all applicable Patent Rights for any Licensed Product being Developed by GSK hereunder that GSK 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 all so-called "Orange Book" listings required under the Hatch-Waxman Act and all so called "Patent Register" listings as required in Canada. Prior to such listings, the Parties will meet, through the Joint Patent Subcommittee, to evaluate and identify all applicable Patent Rights, and GSK shall have the right to review, where reasonable, original records relating to any invention for which Patent Rights are being considered by the Joint Patent Subcommittee for any such listing. Notwithstanding the preceding sentence, GSK will retain final decision making authority as to the listing of all applicable Patent Rights for such Licensed Product, regardless of which Party owns such Patent Right, and any such final decision made in good-faith on the matter shall not be subject to any further review under Section 13.1 or otherwise under this Agreement.

8.7.2 *Regulus' Obligations*. To the extent required or permitted by law, Regulus will use Diligent Efforts to promptly, accurately and completely list, with the applicable Regulatory Authorities during the Agreement Term, all applicable Patent Rights for any Refused Candidate Products and Returned Licensed Products being Developed by Regulus hereunder that Regulus 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 all so-called "Orange Book" listings required under the Hatch-Waxman Act and all so called "Patent Register" listings as required in Canada. Prior to such listings, the Parties will meet, through the Joint Patent Subcommittee, to evaluate and identify all applicable Patent Rights, and Regulus shall have the right to review, where reasonable, original records relating to any invention for which Patent Rights are being considered by the Joint Patent Subcommittee for any such listing. Notwithstanding the preceding sentence, Regulus will retain final decision making authority as to the listing of all applicable Patent Rights for such Refused Candidate Product or Returned Licensed Product, as applicable, regardless of which Party owns such Patent Right, and any such

final decision made in good-faith on the matter shall not be subject to any further review under Section 13.1 or otherwise under this Agreement.

8.8 CREATE Act. Notwithstanding anything to the contrary in this Article 8, neither Party shall 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 8 without the prior written consent of the other Party, which shall not be unreasonably withheld, conditioned or delayed. With respect to any such permitted election, the Parties shall 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.

8.9 Obligations to Third Parties. Notwithstanding any of the foregoing, each Party's rights and obligations with respect to Regulus Technology under this Article 8 shall be subject to Third Party and Parent-Originated Rights and Obligations.

8.10 Additional Right. Notwithstanding any provision of this Article 8, Isis will actively participate in the planning and conduct of any enforcement of Regulus Technology and will take the lead of such enforcement solely to the extent that the scope or validity of any Parent Company Patent

Controlled by Isis and covering a [***] chemical modification is at risk. Such Parent Company Patents Controlled by Isis as of the Effective Date are set forth on Schedule 8.10.

ARTICLE 9

CONFIDENTIALITY

9.1 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 [***] years thereafter, the receiving Party (the "**Receiving Party**"), its Affiliates and, with respect to Regulus, its Parent 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 Parent 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 Parent 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:

9.1.1 was in the lawful knowledge and possession of the Receiving Party, its Affiliates or Parent Companies prior to the time it was disclosed to, or learned by, the Receiving Party, its Affiliates or Parent Companies, or was otherwise developed independently by the Receiving Party, its Affiliates or Parent 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 Parent Companies;

9.1.2 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 Parent Companies;

9.1.3 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 Parent Companies in breach of this Agreement; or

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

9.2 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 Parent 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 Collaboration Compounds, Licensed Products, Refused Candidates, Refused Candidate Products and/or Returned Licensed 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 9.6 below),

complying with applicable governmental regulations, obtaining Regulatory 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 or Parent Companies 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 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) 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 Parent Company's licensor with respect to any intellectual property licensed under this Agreement; or (v) to the extent mutually agreed to in writing by the Parties. If a Parent Company receives GSK's Confidential Information as permitted pursuant to this Section 9.2, such Parent Company may only use and disclose GSK's Confidential Information solely in accordance with this Section 9.2 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, (y) for such Parent Company to perform its obligations in connection with this Agreement (including without limitation the provision of services to Regulus under the Services Agreement) or the Side Agreement, or (z) for such Parent Company to make a determination to exercise, and to exercise, any of its rights with respect to Refused Candidates, Refused Candidate Products or Returned Licensed Products under the JV Agreements.

9.3 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 G. Except to the extent required to comply with applicable law, regulation, rule or legal process or as otherwise permitted in accordance with this Section 9.3, neither Party nor such Party's Affiliates or Parent Companies shall make any public announcements, press releases or other public disclosures concerning this Agreement, the Side Agreement or the Convertible Promissory Note, 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) each Commercializing Party, its Affiliates and Parent Companies may, without the other Party's

approval, make disclosures pertaining solely to its Royalty-Bearing Products, provided, however, that the Commercializing Party will immediately notify (and provide as much advance notice as possible to) the other Party of any event materially related to such other Party's Royalty-Bearing Products (including any Regulatory 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 any Party related to efficacy or safety data and/or results of a Royalty-Bearing Product will be submitted to the other Party for review at least [***] Business Days (to the extent permitted by law) in advance of such proposed public disclosure, the other Party 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 Parent 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, the Side Agreement or the Convertible Promissory Note to potential, bona fide investors and investment bankers, in each case, where practicable, 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, the Side Agreement or the Convertible Promissory Note 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, the Side Agreement or the Convertible Promissory Note for which confidential treatment should be sought.

9.4 Prior Confidentiality Agreement Superseded. This Agreement supersedes the Confidential Disclosure Agreement executed by Regulus, its Parent Companies and GSK on [***] (including any and all amendments thereto). All information exchanged between the Parties under that agreement shall be deemed Confidential Information hereunder and shall be subject to the terms of this Article 9.

9.5 Remedies. Notwithstanding Section 13.1, 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 9.

9.6 Publications. 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 Diligent 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 shall establish a procedure for publication review and each Party shall first submit to the other Party through the Joint Patent Subcommittee 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. Each Party shall 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 shall 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 patent application, or the public disclosure of such proposed publication could be expected to have a material adverse effect on any Patent Rights or Know-How solely owned or Controlled by such other Party, then such Party shall 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. The Parties agree that all publications of results of the Development activities by either Party shall acknowledge the contribution of the other Party, its Affiliates, Parent Companies and Third Party collaborators, as applicable, to such results.

ARTICLE 10

REPRESENTATIONS AND WARRANTIES

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

10.1.1 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;

10.1.2 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;

10.1.3 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;

10.1.4 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;

10.1.5 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 under the Convertible Promissory Note or to obtain HSR clearance; and

10.1.6 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 Collaboration Compounds and related Licensed Products and its activities under each Program.

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

10.2.1 To the best of its knowledge and belief, without having conducted any special inquiry, 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 Technology under this Agreement for all Programs hereunder;

10.2.2 To the best of its knowledge and belief, without having conducted any special inquiry, Regulus does not require any additional licenses or other intellectual property

rights owned by any of its Parent Companies in order for Regulus to conduct the identification, research, optimization and other Development activities contemplated to be conducted by Regulus with respect to human therapeutics pursuant to the Programs hereunder;

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

10.2.4 Regulus has not withheld from GSK any material data or any material correspondence, including to or from any Regulatory Authority, in Regulus' possession as of the Effective Date that would be material and relevant to a reasonable assessment of the scientific, commercial, safety, regulatory and commercial liabilities and commercial value of the collaboration between the Parties and any Collaboration Compound hereunder.

10.3 Regulus Covenants. Regulus hereby covenants to GSK that:

10.3.1 all employees of Regulus and all employees of Regulus' Parent Companies or Affiliates performing Development activities hereunder on behalf of Regulus shall be obligated to assign all right, title and interest in and to any inventions developed by them, whether or not patentable, to Regulus or such Parent Company or Affiliate, respectively, as the sole owner thereof, and each Parent Company shall be obligated under the Services Agreement to assign all right, title and interest in and to any such inventions developed by its employees, whether or not patentable, to Regulus thereunder;

10.3.2 Regulus shall, as appropriate, hire and maintain sufficient staff and management to meet its Diligent Efforts in order to support and conduct all the Programs hereunder in a timely fashion, or use its Diligent Efforts to support and conduct certain activities under the Programs hereunder through the Services Agreement;

10.3.3 if reasonably requested by GSK in writing, Regulus will take reasonable, good faith measures and cooperate with GSK to help to facilitate a good faith negotiation between GSK and any Parent Company or Third Party licensor of Regulus under the agreements listed on Exhibit F hereto (collectively, the "**Existing In-License Agreements**") in the event that GSK desires to pursue the Development or Commercialization of any Collaboration Compound or Licensed Product and would require a license directly from any such Third Party, unless the Parent Companies have achieved the results described in Section 6 of the Side Agreement with respect to the applicable Existing In-License Agreement;

10.3.4 it will not withhold from GSK any material information or correspondence, including to or from any Regulatory Authority, that would be material and relevant to a reasonable assessment of the scientific, commercial, safety, and regulatory liabilities or commercial value of the Collaboration Compounds and Option Compounds included in a Program for which GSK is considering whether to exercise its Program Option with respect to each Option Compound and the related Collaboration Compounds; and

10.3.5 Regulus shall 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 Regulus, shall at all times comply (and shall ensure compliance by any of its subcontractors or its Parent Companies under the Services Agreement) 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 Regulus shall 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.

10.4 GSK Covenants. GSK hereby covenants to Regulus that:

10.4.1 GSK shall 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, shall at all times comply (and shall 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 Regulus' reasonable right to conduct reasonable inspections (but not to audit) with advance notice, and GSK shall 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; and

10.4.2 GSK shall notify Regulus in writing within [***] Business Days of the date that GSK or its Affiliate [***]. The Parties acknowledge and agree that [***] Compounds shall not trigger the obligation under this covenant.

10.5 DISCLAIMER. EXCEPT AS OTHERWISE EXPRESSLY SET FORTH IN THIS AGREEMENT OR IN THE SIDE 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 PATENTS 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 THE COLLABORATION COMPOUNDS ARE THE SUBJECT OF ONGOING CLINICAL RESEARCH AND DEVELOPMENT AND THAT REGULUS CANNOT ASSURE THE SAFETY, USEFULNESS OR COMMERCIAL OR TECHNICAL VIABILITY OF RESULTING DEVELOPMENT CANDIDATES, OPTION COMPOUNDS, AND/OR LICENSED PRODUCTS.

ARTICLE 11

INDEMNIFICATION; INSURANCE

11.1 Indemnification by GSK. GSK shall indemnify, defend and hold harmless Regulus, and its Affiliates and Parent 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:

11.1.1 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;

11.1.2 any breach of any representation or warranty or express covenant made by GSK under Article 10 or any other provision under this Agreement;

11.1.3 the Development or Manufacturing activities that are conducted by and/or on behalf of GSK or its Affiliates or Sublicensees (which shall exclude any Development or Manufacturing activities that are conducted by and/or on behalf of Regulus hereunder), including handling and storage and manufacture by and/or on behalf of GSK or its Affiliates or Sublicensees of any Collaboration Compounds for the purpose of conducting Development or Commercialization by or on behalf of GSK or its Affiliates or Sublicensees; or

11.1.4 the Commercialization by or on behalf of GSK, its Affiliates or Sublicensees of any Collaboration Compound or Licensed Product pursuant to the exercise by GSK of the relevant Program Option;

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, Parent 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 Parent Companies hereunder, or under the Side Agreement.

11.2 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:

11.2.1 the negligence, recklessness or wrongful intentional acts or omissions of Regulus and/or any of its Parent Companies and/or its or their Affiliates and/or its or their respective directors, officers, employees and agents, in connection with Regulus' performance of its obligations or exercise of its rights under this Agreement or any of its Parent Company's obligations under the Side Agreement;

11.2.2 any breach of any representation or warranty or express covenant made by Regulus under Article 10 or any other provision under this Agreement or made by any of its Parent Companies under the Side Agreement;

11.2.3 the Development or Manufacturing activities actually conducted by or on behalf of Regulus (which shall exclude any Development or Manufacturing activities conducted by or on behalf of GSK hereunder), including the storage and handling and manufacture by and/or on behalf of Regulus and/or its Affiliates, Parent Companies and/or its Sublicensees or subcontractors of any Collaboration Compounds for the purpose of Development or Commercialization by or on behalf of Regulus; or

11.2.4 the Commercialization of any Refused Candidates, Refused Candidate Products or Returned Licensed Products by or on behalf of Regulus and/or its Affiliates, or any of its Parent Companies or its Sublicensees;

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 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.

11.3 Procedure. In the event that any Person entitled to indemnification under Section 11.1 or Section 11.2 (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). The provisions of Section 8.4 shall govern the procedures for responding to a Claim of infringement described therein. Notwithstanding anything in this Agreement to the contrary, the indemnifying Party shall have no liability under Section 11.1 or 11.2, as the case may be, with respect to Claims settled or compromised by the Indemnitee without the indemnifying Party's prior written consent.

11.4 Insurance.

11.4.1 *Regulus' Insurance Obligations*. Regulus shall 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, Regulus shall maintain, in force from thirty (30) days prior to enrollment of the first patient in a Clinical Study, at its sole cost, a general liability insurance policy providing coverage of at least [***] per claim and annual aggregate, provided that such coverage is increased to at least [***] at least thirty (30) days

before Regulus initiates the First Commercial Sale of any Refused Candidate, Refused Candidate Product or Returned Licensed Product hereunder. Regulus shall furnish to GSK evidence of such insurance, upon request.

11.4.2 *GSK's Insurance Obligations*. 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.

11.5 LIMITATION OF CONSEQUENTIAL DAMAGES. EXCEPT FOR A BREACH OF ARTICLE 7 OR ARTICLE 9 OR FOR CLAIMS OF A THIRD PARTY WHICH ARE SUBJECT TO INDEMNIFICATION UNDER THIS ARTICLE 11 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 12

TERM AND TERMINATION

12.1 Agreement Term; Expiration. This Agreement shall be effective as of the Effective Date and shall continue in force and effect during the Collaboration Term and shall continue thereafter until expiration as described in this Section 12.1, unless earlier terminated pursuant to the other provisions of this Article 12, and shall expire as follows:

12.1.1 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 Refused Candidate Products and Returned Licensed Products) in such country;

12.1.2 in its entirety upon the expiration of all payment obligations under this Agreement with respect to the last Licensed Product (including Refused Candidate Products and Returned Licensed Products) in all countries in the Territory pursuant to Section 12.1.1; and

12.1.3 where GSK declines to exercise all of its Program Options on or before the end of the applicable PoC Option Exercise Period for a given Program, on a Program-by-Program basis, the rights and obligations of each Party with respect to such Program shall terminate (except, in each case, subject to Section 12.1.5(c)) upon expiration of the PoC Option Exercise Period with respect to the relevant Program.

12.1.4 The period from the Effective Date until the date of expiration of the entire Agreement or as the case may be, until the date of expiration of the Agreement in part with respect to a given Licensed Product, pursuant to this Section 12.1 shall be the **"Agreement Term**" of the Agreement in its entirety or with respect to a given Licensed Product, respectively.

12.1.5 *Effect of Expiration of the Term.*

(a) Following the expiration of the Agreement Term with respect to a Licensed Product (including any Refused Candidate Product or Returned Licensed Product) in a country pursuant to Section 12.1.1, (i) if GSK is the Commercializing Party, the license granted to GSK pursuant

to Section 5.2.1 with respect to such Licensed Product shall convert to an exclusive (subject to clause (iii) and subparagraph (b) below), fully-paid and royalty-free, right and license, with the right to grant sublicenses (as set forth in Section 5.2.2), under all of Regulus' rights in and to the Regulus Technology and the Collaboration Technology, to continue to Develop, Manufacture and Commercialize such Licensed Product in the Field in such country, for so long as it continues to do so; (ii) if Regulus is the Commercializing Party, the license granted to Regulus pursuant to Section 5.1.2 or 5.1.3, as applicable, with respect to such Refused Candidate Product or Returned Licensed Product, respectively, shall convert to an exclusive (subject to clause (iii) and subparagraph (b) below), fully-paid and royalty-free, right and license, with the right to grant sublicenses (as set forth in Section 5.1.4), under all of GSK's rights in and to the GSK Technology and the Collaboration Technology, solely as necessary to continue to Develop, Manufacture and Commercialize such Refused Candidate Product or Returned Licensed Product in the Field in such country, for so long as it continues to do so; and (iii) any remaining exclusivity obligation under Sections 7.1 and 7.2 (it being understood that such exclusivity obligations may have terminated earlier pursuant to Section 12.7 below) shall no longer apply to bind or restrict either Party or its Affiliates, or Regulus' Parent Companies, with respect to the Collaboration Target against which such Licensed Product, or Refused Candidate Product or Returned Licensed Product, as the case may be, is directed, provided, however, that if

there are other Licensed Products being Developed, Manufactured and/or Commercialized by the Commercializing Party that are directed to such Collaboration Target, and the Agreement Term remains in effect with respect to such Licensed Products, then, subject to the remainder of this Article 12, this clause (iii) shall not apply unless and until the Agreement Term has expired with respect to all such Licensed Products.

(b) [Intentionally Left Blank]

(c) Where GSK declines to exercise all of its Program Options for a given Program, on a Program-by-Program basis, on or before the end of the applicable PoC Option Exercise Period, then, following the lapse of such Program Options with respect to such Program pursuant to Section 12.1.3, subject to the applicable terms and conditions of this Agreement, (i) such Program(s) shall be deemed terminated hereunder, (ii) the exclusive license granted to Regulus pursuant to Section 5.1.2 shall apply with respect to any Refused Candidates and Refused Candidate Products resulting from such terminated Program(s), (iii) Regulus shall be obligated to make Reverse Royalty payments to GSK in accordance with Section 6.7 with respect to any Refused Candidate Products resulting from such terminated Program(s), (iv) GSK shall have no further rights in, or options to, any Collaboration Compounds Developed under (or Licensed Products resulting from) such terminated Program(s), (v) Regulus shall have no further obligation to GSK to perform any Development activities hereunder with respect to such Program(s), (vi) Regulus shall not be required to comply with any diligence obligations with respect to any Refused Candidates or Refused Candidate Products resulting from such terminated Program(s), (vii) all licenses granted hereunder to GSK with respect to such Program(s), or any Collaboration Compounds Developed under (or Licensed Products resulting from) such terminated Program(s), shall terminate and be of no further force and effect, (viii) any remaining exclusivity obligation set forth in Section 7.1 or 7.2 shall terminate with respect to the Collaboration Target to which such terminated Program(s) was directed, and (ix) during a period not to exceed [***] months thereafter, GSK will promptly deliver or disclose, as appropriate, to Regulus, at no cost to Regulus, (A) all the pre-clinical and clinical data and results (including pharmacology, toxicology, emulation and stability studies), adverse event data, protocol results, analytical methodologies, arising from the Enabling Studies, (B) copies of patent applications and patents included within GSK Enabling Studies Patents, and (C) regulatory filings (including all relevant INDs and Regulatory Approvals), regulatory documentation, regulatory correspondence, and applicable reference standards with respect to the Enabling Studies, ownership of which regulatory filings shall be transferred to Regulus or, if such transfer is not reasonably practical, a right of reference shall be granted to Regulus.

12.2 Termination for Cause.

12.2.1 *During the Collaboration Term and Prior to any GSK Exercise of Program Options*. Except as set forth in Section 12.2.3 or Section 12.2.4, 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 during the Collaboration Term prior to GSK's exercise of a Program Option, on a Collaboration Target-by-Collaboration Target basis, or in its entirety in the case of a material breach that pertains to the Agreement as a whole or with respect to [***] or more Collaboration Targets to protect the interest of the Non-Breaching Party arising from such alleged breach, 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 either with respect to such Collaboration Target, or the Agreement as a whole or with respect to [***] or more Collaboration Targets, as the case may be, 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.

12.2.2 *Following GSK Exercise of a Program Option.* Except as set forth in Section 12.2.3 or 12.2.4 below, 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 its entirety, or in part on a Collaboration Target-by-Collaboration Target basis, following GSK's exercise of a Program Option with respect to the relevant Program, 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 either with respect to such Collaboration Target, or, for a termination of the entire Agreement, for a material breach which relates either to [***] Collaboration Targets or which pertains to the Agreement as a whole, 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.

12.2.3 *Termination by GSK due to a Regulus Diligence Failure Event or Regulus Exclusivity Breach.* In the event that Regulus materially breaches its diligence obligations under Section 3.6 (a "**Regulus Diligence Failure Event**") or its exclusivity obligations under Section 7.1 or 7.2 (a "**Regulus Exclusivity Breach**"), and Regulus fails to cure such material breach in accordance with the provisions for notice and cure as set forth under Section 12.2.1 or Section 12.2.2, as applicable, and the provisions for dispute resolution as set forth under Section 12.2.5, GSK shall have the right, at its sole discretion, to terminate the Agreement in part on a Program-

by-Program basis or in its entirety (in the case of an uncured Regulus Diligence Failure Event [***] or a Regulus Exclusivity Breach for any Program). The rights and obligations of the respective Parties in the event of termination by GSK for an uncured Regulus Diligence Failure Event or a Regulus Exclusivity Breach shall be as specifically set forth in Section 12.7.3(c) below and/or in the Side Agreement. Notwithstanding anything in this Agreement to the contrary, such termination by GSK, and the consequences set forth in Section 12.7.3(c) below and/or in the Side Agreement, shall be [***] with respect to any Regulus Diligence Failure Event.

12.2.4 *Termination by Regulus due to a GSK Diligence Failure Event*. In the event that, after the exercise by GSK of its Program Option for a Program, GSK materially breaches its diligence obligation under Section 4.4.1 (a **"GSK Diligence Failure Event"**), and GSK fails to cure such material breach in accordance with the provisions for notice and cure as set forth under Section 12.2.1 or Section 12.2.2, as applicable, and the provisions for dispute resolution as set forth under Section 12.2.5, then Regulus shall have the right, at its sole discretion, to terminate this Agreement in part on a Collaboration Target-by-Collaboration Target basis or in its entirety (in the case of an uncured GSK Diligence Failure Event [***]). The rights and obligations of the respective Parties in the event of termination by Regulus for an uncured GSK Diligence Failure Event shall be as specifically set forth in Section 12.7.4 below. Notwithstanding anything in this Agreement to the contrary, such termination by Regulus, and the consequences set forth in Section 12.7.4 below, shall be [***] with respect to any GSK Diligence Failure Event.

12.2.5 *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 12.2.1, Section 12.2.2, Section 12.2.3 or Section 12.2.4 above, the Party which seeks to dispute that there has been a material breach may contest the allegation in accordance with Section 13.1. 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, except that such cure period shall be tolled (as more specifically set forth in Section 12.7.3(d) or Section 12.7.4(b), as applicable) during the pendency of any arbitration with respect to a dispute concerning any Regulus Diligence Failure Event or a Regulus Exclusivity Breach under Section 12.2.3, or a GSK Diligence Failure Event under Section 12.2.4. Subject to Section 12.7.3(d) and 12.7.4(b), any termination of the Agreement under this Section 12.2 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, or a Collaboration Target(s) under this Agreement, as provided in this Section 12.2 shall not be affected in any way by such Party's waiver or failure to take action with respect to any previous default.

12.3 GSK Unilateral Termination Rights. GSK shall have the right, at its sole discretion, exercisable at any time during the Agreement Term, to terminate this Agreement in its entirety or in part on a Collaboration Target-by-Collaboration Target basis, for any reason or for no reason at all, upon [***] days written notice to Regulus, subject to the rights and obligations of the Parties set forth in Sections 12.7.1, 12.7.6, 12.7.7 and 12.8. Except as set forth in Section 12.7.1, 12.7.6, 12.7.7 or 12.8, GSK shall not have any additional cost, liability, expense, or obligation of any kind whatsoever on account of any termination under this Section 12.3. Notwithstanding the above, in the event of a disagreement between the Parties regarding safety concerns where GSK believes in good faith that such concerns merit the immediate termination of a Program, GSK shall have the right pursuant to this Section 12.3 to terminate such Program immediately upon written notice to Regulus and without the [***] day notice period for termination. For purposes of clarity, in no event shall GSK have the right to exercise its right to terminate the Agreement under this Section 12.3 following Regulus' notice of termination under Section 12.2, 12.4 or 12.6.

12.4 Regulus' Limited [***] Termination Rights. Regulus shall have the right, exercisable upon written notice to GSK and at Regulus' sole discretion, to immediately terminate one or more Collaboration Targets or the entire Agreement (in which event Section 12.7.2 shall apply), but only in the event that GSK or one of its Affiliates [***]; provided, however, that such termination right shall not apply in the event that [***]. Regulus shall only be permitted to exercise such termination right until the date that is [***] months from the date that GSK or its Affiliate [***] or within [***] months of the date that GSK notifies Regulus that GSK or its Affiliate has [***] accordance with Section 10.4.2, whichever is latest. The Parties acknowledge and agree [***] shall not trigger Regulus' termination right under this Section 12.4. For purposes of this Section 12.4, an [***].

12.5 Termination Pursuant to JSC or [***] or Otherwise under Section 3.4.3. In the event that the JSC [***] decides to terminate a Program, on a Program-by-Program basis, due to [***], or in the event that a Program otherwise terminates under Section 3.4.3, the Agreement shall terminate with respect to such Program as set forth in Section 12.7.5, subject to the exercise by GSK of its Terminated Program Option under Section 4.2.3 and its rights and obligations pursuant thereto.

12.6 Termination for Insolvency.

12.6.1 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.

12.6.2 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.

12.6.3 If GSK terminates this Agreement pursuant to Section 12.6.1, the provisions of Section 12.7.3 shall apply.

12.6.4 If Regulus terminates this Agreement pursuant to Section 12.6.1, the provisions of Section 12.7.4 shall apply.

12.7 Effects of Termination.

12.7.1 *Upon Unilateral Termination by GSK under Section 12.3.* In the event of a unilateral termination of this Agreement by GSK in its entirety or with respect to any Collaboration Target(s) pursuant to Section 12.3:

(a) Notwithstanding anything contained herein to the contrary, all licenses granted to GSK with respect to Collaboration Compounds and Licensed Products directed to such terminated Collaboration Target(s) shall terminate, and all such Collaboration Compounds and Licensed Products shall be deemed Refused Candidates, Refused Candidate Products or (if GSK has previously exercised its Program Option as of the effective date of such termination) Returned Licensed Products, and the exclusive licenses granted to Regulus under

Section 5.1.2 and Section 5.1.3 shall apply with respect to such Refused Candidates and Refused Candidate Products, and Returned Licensed Products, respectively;

(b) the Reverse Royalty payment obligations of Regulus under Section 6.7 with respect to any Refused Candidate Products or Returned Licensed Products shall apply, subject to Section 12.7.7;

(c) Regulus shall have no further obligation to GSK to perform any Development or Manufacturing activities hereunder with respect to the terminated Collaboration Target(s);

(d) GSK shall have no further obligation to Regulus to perform any Development, Manufacturing or Commercialization activities hereunder with respect to the terminated Collaboration Target(s), except as set forth in Section 12.7.6;

(e) Regulus shall not be required to comply with any diligence obligations with respect to any Refused Candidates, Refused Candidate Products or Returned Licensed Products directed to such terminated Collaboration Target(s);

(f) All Program Options that are not exercised by GSK under Section 4.2 with respect to any Program(s) terminated under this Section 12.7.1 before the date of GSK's notice of termination shall be cancelled and of no force and effect;

(g) All of Regulus' and GSK's exclusivity obligations (including those of each Party's Affiliates and, with respect to Regulus, Parent Companies) under Article 7 shall immediately terminate and no longer be of any force or effect with respect to the Collaboration Target(s) being terminated (including all Collaboration Compounds and Licensed Products directed to such terminated Collaboration Target(s)); and

(h) Section 12.7.6 shall apply.

12.7.2 *Upon Unilateral Termination by Regulus under Section 12.4; Termination by Regulus for [***]* In the event of any unilateral termination by Regulus of this Agreement in its entirety or with respect to any Collaboration Target(s) in accordance with Section 12.4, or a termination by Regulus of this Agreement in its entirety or with respect to any Collaboration Target(s) in accordance with Section 12.2 for an uncured material breach by GSK of [***], then and in such event:

(a) Notwithstanding anything contained herein to the contrary, all licenses granted to GSK with respect to Collaboration Compounds and Licensed Products directed to such terminated Collaboration Target(s) shall terminate and all such Collaboration

Compounds and Licensed Products shall be deemed Refused Candidates, Refused Candidate Products or (if GSK has previously exercised its Program Option as of the effective date of such termination) Returned Licensed Products, as applicable, and the exclusive licenses granted to Regulus under Section 5.1.2 and Section 5.1.3 shall apply with respect to such Refused Candidates and Refused Candidate Products, and Returned Licensed Products, respectively;

(b) Such termination shall be without any right of GSK to receive from Regulus, or any obligation of Regulus to pay to GSK, any Reverse Royalties which would otherwise be applicable under Section 6.7 with respect to such Refused Candidates and Refused Candidate Products, and Returned Licensed Products;

(c) Regulus shall have no further obligation to GSK to perform any Development or Manufacturing activities hereunder with respect to the terminated Collaboration Target(s);

(d) GSK shall have no further obligation to Regulus to perform any Development, Manufacturing or Commercialization activities hereunder with respect to the terminated Collaboration Target(s), except as set forth in Section 12.7.6;

(e) Regulus shall not be required to comply with any diligence obligations with respect to any Refused Candidates, Refused Candidate Products or Returned Licensed Products directed to such terminated Collaboration Target(s);

(f) All Program Options that are not exercised by GSK under Section 4.2 with respect to any Program(s) terminated under this Section 12.7.2 before the date of Regulus' notice of termination shall be cancelled and of no force and effect;

(g) All of Regulus' and GSK's exclusivity obligations (including those of each Party's Affiliates and, with respect to Regulus, Parent Companies) under Article 7 shall immediately terminate and no longer be of any force or effect with respect to the Collaboration Target(s) being terminated (including all Collaboration Compounds and Licensed Products directed to such terminated Collaboration Target(s)); and

(h) Section 12.7.6 shall apply.

12.7.3 *Upon Termination by GSK for Cause under Section 12.2; Termination by GSK for Regulus Insolvency under Section 12.6.* In the event of a termination of this Agreement either in its entirety or on a Program-by-Program basis by GSK pursuant to Section 12.2 or 12.6, then for each Program, subparagraph (a) shall apply for all such Programs for which GSK has not exercised its Program Option, and subparagraph (b) shall apply for all such Programs for which GSK has exercised its Program Option, except that for all Programs for which (i) a

Regulus Diligence Failure Event has occurred or (ii) a Regulus Exclusivity Breach has occurred, subsection 12.7.3(c) shall apply.

(a) For each Program which is terminated by GSK under Section 12.2.1, or under Section 12.6 if GSK has not exercised its Program Option with respect to such Program, then:

(i) The Collaboration Term shall terminate with respect to such terminated Collaboration Target(s) with no additional amounts owed to Regulus (except as set forth in clause (v) below or in Section 12.8);

(ii) Notwithstanding anything contained herein to the contrary, GSK shall have and Regulus hereby grants, conditional upon such event, with respect to each Program terminated under this subparagraph (a), the exclusive licenses granted to GSK under Section 5.2.1 with respect to the Collaboration Target, Collaboration Compounds, Option Compounds, and Licensed Products resulting from such Program, and, depending upon the progress of such Program as of the date of such termination, the scope of such license shall be modified as necessary in accordance with the clarifications stated in Section 12.7.7(d), which exclusive license shall become effective immediately upon the termination of such terminated Program(s);

(iii) If the Regulus uncured material breach or Regulus insolvency occurs with respect to such Program prior to the final selection of the [***] Collaboration Targets in accordance with Section 3.2, GSK shall have the right to select, within the [***] period following any such termination, the remaining [***] final Collaboration Targets (from the miRNA Pool or, if the miRNA Pool has not been finalized as of the effective date of termination, the miRNA Library, but in each case excluding any Blocked Targets), upon the final selection of which GSK shall have and Regulus hereby grants, conditional upon such event, the exclusive, worldwide and sublicenseable license described in Section 5.2.1, with respect to the Collaboration Target and any Collaboration Compounds, Option Compounds, and Licensed Products resulting from such Program, and the scope of such license shall be modified as necessary in accordance with the clarifications stated in Section 12.7.7(d). Such exclusive license shall become effective with respect to such final Collaboration Targets and any miRNA Antagonists, miRNA Compounds and miRNA Therapeutics directed to any such final Collaboration Target in the Field;

(iv) in no event shall any Collaboration Compounds Developed under such terminated Program(s) be deemed Refused Candidates, nor shall any Licensed Products containing any such Collaboration Compound(s) as an active ingredient(s) be deemed

Refused Candidate Products, to which Regulus would otherwise have rights under Section 4.2.7 of this Agreement;

(v) GSK shall (A) be obligated to pay Regulus [***] of any [***] that would otherwise be payable under [***] upon the acquisition by GSK of an exclusive license to the Collaboration Compounds resulting from the terminated Program(s) in accordance with the applicable provisions of this Article 12 for the terminated Program(s) under clause (ii), (iii) of this Section 12.7.3(a), and (B) be obligated to pay Regulus [***] subject to Section [***]; such that, in the case of each of clause (A) or (B) above, if the Leading Compound has not yet reached [***] shall apply, but reduced by [***], and if the Leading Compound has entered a [***] but has not [***], then [***] shall apply, but reduced by [***], and if a [***] has been Initiated, then [***] shall apply, but reduced by [***] in each case (1) with respect to the Collaboration Compounds and Licensed Products resulting from the terminated Program(s) for which GSK acquires such exclusive license under clause (ii) or clause (iii) hereof, including any miRNA Antagonists, miRNA Compounds and miRNA Therapeutics directed to the final [***] Collaboration Targets selected under clause (iii) of this Section 12.7.3(a) (which miRNA Antagonists, miRNA Compounds and miRNA Therapeutics shall be deemed Collaboration Compounds and Licensed Products for purposes of determining the royalties payable to Regulus hereunder), and (2) in no event shall the [***] hereunder be less than [***] of [***] [***] with respect to Licensed Products resulting from the terminated Program(s) for which GSK acquires an exclusive license pursuant to the provisions of this Section 12.7.3(a). Notwithstanding any other provision under this Agreement or the Side Agreement, or any of the JV Agreements, or any interpretation of any one or any combination of the above to the contrary, no [***] shall be owed to Regulus, its Affiliates or to any of Regulus' Parent Companies, successors or assigns on account of the exclusive license acquired by GSK as described in this Section 12.7.3(a) as clarified in section 12.7.7(d), and the provisions of Article 6 regarding milestone and royalty payments shall not apply, except as expressly set forth in this Section 12.7.3(a);

(vi) Regulus shall have no further obligation to GSK to perform any Development or Manufacturing activities hereunder with respect to such terminated Collaboration Targets (including any of the [***] final Collaboration Targets selected by GSK under clause (iii) above), except in the event that GSK exercises its Program Option under clause (ii) or (iii) above, in which case Section 5.3 shall apply;

(vii) GSK shall not be required to comply with any diligence obligations with respect to the terminated Collaboration Target(s) (including any of the [***] final Collaboration Targets selected by GSK under clause (iii) above); and

(viii) All of Regulus' and GSK's exclusivity obligations (including those of each Party's Affiliates and, with respect to Regulus, Parent Companies) under Article 7 shall immediately terminate and no longer be of any force or effect with respect to the Collaboration

Target(s) (including any of the final [***] Collaboration Targets selected by GSK under clause (iii) above) being terminated (including all Collaboration Compounds and Licensed Products directed to such terminated Collaboration Target(s)).

(b) For each Program which is terminated by GSK pursuant to Section 12.2.2 or under Section 12.6 if GSK has exercised its Program Option with respect to such Program, then:

(i) The Agreement shall terminate with respect to such terminated Collaboration Target(s) with no additional amounts owed to Regulus (except as set forth in clause (iii) below or in Section 12.8);

(ii) Notwithstanding anything contained herein to the contrary, GSK shall have or retain and, if not earlier granted, Regulus hereby grants, conditional upon such event, with respect to any Program(s) terminated under subparagraph (b) above, the exclusive licenses granted to GSK under Section 5.2.1 with respect to the Collaboration Target, Collaboration Compounds, Option Compounds, and Licensed Products resulting from such Program;

(iii) in no event shall any Collaboration Compounds Developed under such terminated Program(s) be deemed Refused Candidates, nor shall any Licensed Products containing any such Collaboration Compound(s) as an active ingredient(s) be deemed Refused Candidate Products, to which Regulus would otherwise have rights under Section 4.2.7 of this Agreement;

(iv) GSK shall (A) be obligated to pay Regulus [***] of any [***] under the Agreement that would otherwise be payable under Section [***], subject to Section [***], with respect to the terminated Program(s) under this Section 12.7.3(b), and (B) be obligated to pay Regulus [***] of the [***], as applicable, under the relevant Program Option in accordance with Section 4.2, in each case (1) with respect to the Collaboration Compounds and Licensed Products resulting from the terminated Program(s) for which GSK retains or acquires such exclusive license under clause (ii) hereof, and (2) in no event shall the [***] of [***] with respect to Licensed Products resulting from the terminated Program(s) for which GSK acquires an exclusive license pursuant to the provisions of this Section 12.7.3(b). Notwithstanding any other provision under this Agreement or the Side Agreement, or any of the JV Agreements, or any interpretation of any one or any combination of the above to the contrary, [***] shall be

owed to Regulus, its Affiliates or to any of Regulus' Parent Companies, successors or assigns on account of the exclusive license acquired by GSK as described in this Section 12.7.3(b) as clarified in section 12.7.7(d), and the provisions of Article 6 regarding [***] shall not apply, except as expressly set forth in this Section 12.7.3(b);

(v) Regulus shall have no further obligation to GSK to perform any Development or Manufacturing activities hereunder with respect to such terminated Collaboration Target(s), except pursuant to Section 5.3;

(vi) GSK shall not be required to comply with any diligence obligations with respect to the terminated Collaboration Target(s) or any Collaboration Compounds, Option Compounds or Licensed Products directed thereto;

(vii) All of Regulus' and GSK's exclusivity obligations (including those of each Party's Affiliates and, with respect to Regulus, Parent Companies) under Article 7 shall immediately terminate and no longer be of any force or effect with respect to the Collaboration Target(s) being terminated (including all Collaboration Compounds and Licensed Products directed to such terminated Collaboration Target(s)); and

(viii) Notwithstanding anything contained herein to the contrary, all licenses granted to GSK under Article 5 with respect to Collaboration Compounds, Option Compounds or Licensed Products directed to the Collaboration Target that is the subject of any Program(s) for which GSK has previously exercised its Program Option as of the effective date of such termination, and which were not directed to the same Collaboration Target as the Program to which the Regulus uncured material breach relates, shall continue in full force, in accordance with the terms and conditions of this Agreement, including without limitation, GSK's payment obligations under Article 6 with respect to any Collaboration Compounds, Option Compounds or Licensed Products resulting from such Program(s).

(c) In the case of a termination by GSK of any Program(s) or the entire Agreement under Section 12.2 as a result of (i) an [***] then the effects set forth in Section 12.7.3(a) or 12.7.3(b) above shall apply, as applicable depending upon whether GSK had exercised its Program Option for such Program, except that GSK shall be obligated to pay Regulus, in lieu of the royalties set forth in Section 12.7.3(a) or Section 12.7.3(b), a [***] with respect to Licensed Products resulting from the terminated Program(s) for which GSK acquires an exclusive license pursuant to the provisions of this Section 12.7.3. Notwithstanding any other provision under this Agreement or the Side Agreement, or any of the JV Agreements, or any interpretation of any one or any combination of the above to the contrary, no milestone payments or other fees, costs, other royalties or payments of any kind shall be owed to Regulus, its

Affiliates or to any of Regulus' Parent Companies, successors or assigns on account of the exclusive license acquired by GSK as described in this Section 12.7.3 as clarified in section 12.7.7(d), and the provisions of Article 6 regarding milestone and royalty payments shall not apply, except as expressly set forth in this Section 12.7.3(c).

(d) *Dispute.* Notwithstanding anything in this Agreement to the contrary, in the event that Regulus disputes the allegation of a Regulus Diligence Failure Event in good faith and pursues such dispute in accordance with Section 13.1, upon initiation of the arbitration process as described in Section 13.1, (i) the cure period set forth in Section 12.2.1 or 12.2.2, as applicable, shall be tolled until the conclusion of the arbitration process and, if such conclusion is in GSK's favor, such cure period shall be extended as set forth in clause (A) below, and (ii) GSK shall be granted the licenses set forth in Section 5.2.1 solely for [***]; provided, however, that (A) upon the conclusion of the arbitration process in GSK's favor, if Regulus fails to comply with the arbitrator's final award on or before the end of the sixty (60) day period following the end of the initial cure period (as tolled as set forth in clause (i) above), termination shall become effective under Section 12.2.3 and the [***] license granted under clause (ii) above shall automatically convert to an exclusive license, with the right to grant sublicenses as set forth in Section 5.2.2, and (B) upon the conclusion of the arbitration process in Regulus' favor, or Regulus' compliance with the arbitrator's final award within the cure period set forth in clause (A) above if the conclusion is in GSK's favor, the [***] license

granted under clause (ii) above shall terminate and revert to Regulus. During the entire time pending the final resolution of any such dispute, Regulus shall not grant any license to any Third Party under the Regulus Technology or Collaboration Technology with respect to the same subject matter, which would materially conflict or otherwise materially interfere with the potential exclusive license to GSK under this Section 12.7.3(d).

(e) The Parties understand and agree that, due to the nature of the collaboration under this Agreement, damages to GSK resulting from [***] Event under this Agreement would be difficult to calculate accurately, and thus the remedy set forth in Sections [***] represents a rational relationship between the damages from [***] on the one hand, and the cumulative loss to GSK of its expectation interest and its lost investment and lost potential return on investment.

12.7.4 *Upon Termination by Regulus for Cause (other than [***] under Section 12.2; Termination by Regulus for GSK Insolvency under Section 12.6.*

(a) In the event of a termination of this Agreement by Regulus pursuant to Section 12.2.1 or 12.2.2, as applicable, with respect to any Collaboration Target(s),

or in its entirety, upon the uncured material breach of GSK [***], in which event Section 12.7.2 shall apply) where such material breach pertains to [***] or more Collaboration Targets, or to the Agreement as a whole, or in the event of a termination of this Agreement in its entirety by Regulus pursuant to Section 12.6 upon the insolvency of GSK:

(i) Notwithstanding anything contained herein to the contrary, all licenses granted to GSK with respect to Collaboration Compounds and Licensed Products directed to such terminated Collaboration Target(s) shall terminate and all such Collaboration Compounds and Licensed Products shall be deemed Refused Candidates, Refused Candidate Products or (if GSK has previously exercised its Program Option as of the effective date of such termination) Returned Licensed Products, and the exclusive licenses granted to Regulus under Section 5.1.2 and Section 5.1.3 shall apply with respect to such Refused Candidates and Refused Candidate Products, and Returned Licensed Products, respectively;

(ii) Regulus shall be obligated to pay GSK any applicable Reverse Royalties under Section [***] with respect to any such Refused Candidate Products, and under Section [***] with respect to any such Returned Licensed Products;

(iii) Regulus shall have no further obligation to GSK to perform any Development or Manufacturing activities hereunder with respect to the terminated Collaboration Target(s);

(iv) GSK shall have no further obligation to Regulus to perform any Development, Manufacturing or Commercialization activities hereunder with respect to the terminated Collaboration Target(s), except as set forth in Section 12.7.6;

(v) Regulus shall not be required to comply with any diligence obligations with respect to any Refused Candidates, Refused Candidate Products or Returned Licensed Products directed to such terminated Collaboration Target(s);

(vi) All Program Options that are not exercised by GSK under Section 4.2 with respect to any Program(s) terminated pursuant to this Section 12.7.4(a) before the date of Regulus' notice of termination shall be cancelled and of no force and effect;

(vii) All of Regulus' and GSK's exclusivity obligations (including those of each Party's Affiliates and, with respect to Regulus, Parent Companies) under Article 7 shall immediately terminate and no longer be of any force or effect with respect to the Collaboration Target(s) being terminated (including all Collaboration Compounds and Licensed Products directed to such terminated Collaboration Target(s)); and

(viii) Section 12.7.6 shall apply.

(b) Notwithstanding anything in this Agreement to the contrary, in the event that GSK disputes the allegation of any GSK Diligence Failure Event in good faith and pursues such dispute in accordance with Section 13.1, upon initiation of the arbitration process as described in Section 13.1, (i) the cure period set forth in Section 12.2.1 or 12.2.2, as applicable, shall be tolled until the conclusion of the arbitration process and, if such conclusion is in Regulus' favor, such cure period shall be extended as set forth in clause (A) below, and (ii) Regulus shall be granted the licenses set forth in Section 5.1.2 or 5.1.3, as the case may be, solely [***]; provided, however, that (A) upon the conclusion of the arbitration process in Regulus' favor, if GSK fails to comply with the arbitrator's final award on or before the end of the sixty (60) day period following the end of the initial cure period (as tolled as set forth in clause (i) above), termination shall become effective under Section 12.2.4 and the [***] license granted under clause (ii) above shall automatically convert to an exclusive license, with the right to grant sublicenses as set forth in Section 5.1.4, and (B) upon the conclusion of the arbitration process in GSK's favor, or GSK's compliance with the arbitrator's final award within the cure period set forth in clause (A) above if the conclusion is in Regulus' favor, the [***] license granted under clause (ii) above shall terminate and revert to GSK. During the entire time pending the final resolution of any such dispute, GSK shall not grant any license to any Third Party under the GSK Technology or Collaboration Technology with respect to the same subject matter, which would materially conflict or otherwise materially interfere with the potential exclusive license to Regulus under this Section 12.7.4(b).

(c) The Parties understand and agree that, due to the nature of the relationship of the Parties under this Agreement, damages to Regulus resulting from a [***] under this Agreement would be difficult to calculate accurately, and thus the remedy set forth in this Section 12.7.4 represents a rational relationship between the damages from the [***] on the one hand, and the cumulative loss to Regulus of its expectation interest and its lost investment and lost potential return on investment.

12.7.5 *Upon Termination by JSC [***] for [***] Otherwise under Section 3.4.3; Terminated Program Options*. In the event that this Agreement is terminated with respect to any Program(s) as a result of a decision of the JSC [***] for [***] concerns, or a Program is otherwise terminated under Section 3.4.3:

(a) Notwithstanding anything contained herein to the contrary, GSK shall have the right, in its sole discretion, to exercise its Terminated Program Option with respect to such terminated Program(s) as set forth in Section 4.2.3, upon which exercise the exclusive licenses granted to GSK under Section 5.2.1 shall become effective with respect to Collaboration

Compounds, Option Compounds and Licensed Products resulting from such terminated Program(s), and the scope of such license shall be as modified and clarified under Section 12.7.7(d);

(b) with respect to any such terminated Program(s) in no event shall any Collaboration Compounds Developed under such terminated Program(s) be deemed Refused Candidates, nor shall any Licensed Products containing any such Collaboration Compound(s) as an active ingredient(s) be deemed Refused Candidate Products, to which Regulus would otherwise have rights under Section 4.2.7 of this Agreement;

(c) GSK shall be obligated to pay Regulus milestones as set forth in Section 6.5.3 and royalties as set forth in Section 6.6.1(d) (subject to Section 6.6.2), in each case depending on the stage of Development at which the termination occurred;

(d) Regulus shall have no further obligation to GSK to perform any Development or Manufacturing activities hereunder with respect to such terminated Program(s) (including any Collaboration Compounds or Licensed Products resulting from such terminated Program(s)), except in the event that GSK exercises its Terminated Program Option under clause (a) above, in which case Section 5.3 shall apply;

(e) GSK shall not be required to comply with any diligence obligations with respect to any Option Compounds or Licensed Products resulting from such terminated Program(s); and

(f) All of Regulus' and GSK's exclusivity obligations (including those of each Party's Affiliates and, with respect to Regulus, Parent Companies) under Article 7 shall immediately terminate and no longer be of any force or effect with respect to such terminated Program(s) (including any Collaboration Compounds and Licensed Products resulting from such terminated Program(s)).

12.7.6 *Technology Transfer.* Upon termination of this Agreement, or any Collaboration Target(s) hereunder, by Regulus pursuant to Section 12.2, 12.4 or 12.6, or by GSK pursuant to Section 12.3, then paragraph (a) below shall apply, and for any termination by GSK pursuant to Section 12.2, 12.5 or 12.6, then Section 5.3 shall apply for all terminated Programs:

(a) If such termination occurs prior to First Commercial Sale of the Licensed Product(s) directed to the terminated Collaboration Target(s), during a period not to exceed [***] months thereafter, GSK will promptly deliver or disclose, as appropriate, to Regulus, [***] to Regulus ([***]), the GSK Technology and Collaboration Technology in GSK's possession or Control to the extent (A) relating specifically and primarily to Refused

Candidates, Refused Candidate Products and/or Returned Licensed Products if such GSK Technology and Collaboration Technology was used in connection with the Program (unless the Parties have mutually agreed to exclude it) or (B) [***] with respect to a specific Collaboration Target that is the subject of such Program, including but not limited to: (i) information regarding the [***], which is necessary for the exercise by Regulus of the Manufacturing rights granted under Section 5.1.2 or 5.1.3, as applicable, (ii) pre-clinical and clinical data and results (including pharmacology, toxicology, emulation and stability studies), adverse event data, protocol results, analytical methodologies, (iii) copies of patent applications and patents included within GSK Patents and GSK Collaboration Patents and other relevant patent information to the extent of any claims directed to subject matter which was used in connection with the Program (unless the Parties have mutually agreed to exclude it) or covering a method of treatment or use with respect to a specific Collaboration Target that is the subject of such Program, (iv) regulatory filings (including all relevant INDs and Regulatory Approvals), regulatory documentation, regulatory correspondence, and applicable reference standards, ownership of which regulatory filings shall be transferred to Regulus or, if such transfer is not reasonably practical, a right of reference shall be granted to Regulus, and (v) at Regulus' request, any then existing supplies as shall be deemed suitable by Regulus of 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 Refused Candidates, Refused Candidate Products or Returned Licensed Products, at GSK's Fully Absorbed Cost of Goods; in each case above to the extent pertaining specifically to any Refused Candidates, Refused Candidate Products and Returned Licensed Products and which are necessary to enable Regulus to Develop, Manufacture and Commercialize such Refused Candidates, Refused Candidate Products and/or Returned Licensed Products in the Field in the Territory. In addition, the Parties will consider in good faith from time to time whether a safety data exchange agreement is required. Without limiting any of the foregoing, GSK shall use Diligent Efforts to perform the transfer of such information and materials to Regulus in an orderly manner, and, upon delivery or disclosure, as appropriate, of such information and materials to Regulus, Regulus shall use Diligent Efforts to promptly implement such information and materials into its Development and Commercialization activities with respect to such Refused Candidates, Refused Candidate Products and/or Returned Licensed Products hereunder. For the avoidance of doubt, the obligation on GSK to deliver or disclose, as appropriate, to Regulus the GSK Technology and other Know-How and information to the extent relating specifically and primarily to Refused Candidates, Refused Candidate Products and/or Returned Licensed Products if such GSK Technology and Collaboration Technology was used in connection with the Program (unless the

Parties have mutually agreed to exclude it), or covering a method of treatment or use with respect to a specific Collaboration Target that is the subject of such Program, in accordance with this Section 12.7.6 shall include (x) the transfer or license of any GSK Technology in the possession of any GSK Affiliate engaged by GSK as a subcontractor in accordance with Section 3.10, and (ii) the use of Diligent Efforts to transfer or license any GSK Technology in the possession of any Third Party subcontractor engaged by GSK as a subcontractor in accordance with Section 3.10.

(b) If termination occurs following First Commercial Sale of the Licensed Product(s) directed to such terminated Collaboration Target(s), with respect to all affected countries, in addition to the items listed in clause (a) above, to the extent that GSK owns any trademark(s) that are specific to any Licensed Product(s), if GSK has used any such trademark extensively, publicly and exclusively in connection with the Licensed Product(s) and not any other products of GSK which are not Licensed Product(s), then GSK agrees to assign such trademark to Regulus, in each country where the Agreement is terminated with respect to such Licensed Product and where GSK has rights in the trademark. In such event, Regulus shall be responsible for recording the assignment in a timely manner and for any and all costs associated with the assignment and recordation in such country.

(c) In addition to clause (a) or (b), GSK shall provide for reasonable transitional support, at [***], up to a maximum of [***], as is reasonably required by Regulus, for up to an additional [***] months with respect to Returned Licensed Products, and any additional support as reasonably required by Regulus shall be charged to Regulus at rates to be agreed between the Parties.

12.7.7 *Special Consequences for Certain Scenarios and Clarifications*

(a) Notwithstanding anything in this Agreement to the contrary, if GSK unilaterally terminates this Agreement under Section 12.3 in its entirety or with respect to any Collaboration Target(s) and in the absence of an uncured material breach of the Agreement by Regulus with respect to such Collaboration Target(s), and GSK or its Affiliates or sublicensees [***], then Regulus shall no longer be obligated to [***] with respect to any Refused Candidate Products or Returned Licensed Products to which Regulus obtains rights under Section 12.7.1 arising from such termination of this Agreement by GSK pursuant to Section 12.3.

(b) In addition, if, at any time prior to any termination of this Agreement with respect to any Collaboration Target(s) and in the absence of an uncured material breach of the Agreement by Regulus with respect to such Collaboration Target(s), GSK or its

Affiliates or sublicensees [***] and then GSK unilaterally terminates this Agreement under Section 12.3 in its entirety or with respect to any Collaboration Target(s), then the consequences of termination set forth in clause (a) above shall apply.

(c) For clarity, upon termination of any Collaboration Target or Program under Article 12 or Section 3.4.3 or 4.2.3, or where GSK declines to exercise all of its Program Options on or before the end of the applicable PoC Option Exercise Period for a given Program, the exclusivity obligations under Section 7.1 or Section 7.2 shall no longer apply to bind or restrict GSK or its Affiliates, or Regulus or its Affiliates or Parent Companies, with respect to the terminated Collaboration Target or Program.

(d) For the sake of clarity, the Parties understand and agree that, in the event that pursuant to the provisions of Sections 12.7.3(a), 12.7.3(c) or 12.7.5, GSK acquires an exclusive license from Regulus under Section 5.2.1 with respect to a terminated Program and the Collaboration Target and Collaboration Compounds relating to such Program, then, if such Program as of the date of such termination has not yet progressed to the point where any Collaboration Compounds at all or any Development Candidates or any Option Compounds or Licensed Products have been identified, then, notwithstanding any interpretation of Section 5.2.1 or any other provision of this Agreement or the Side Agreement or any of the JV Agreements or any combination of any of those to the contrary, GSK shall have the exclusive, sublicenseable right and license in the Field and in the Territory, under the exclusive license granted in Section 5.2.1, to use the Regulus Technology and Regulus' rights in the Collaboration Technology, to identify and discover new (as well as any then-existing) Collaboration Compounds directed to such Collaboration Target, and to Develop, Manufacture and Commercialize any new and existing Collaboration Compounds as and into Licensed Products, and the license granted to GSK under Section 5.2.1 shall not be construed as limiting GSK only to use Regulus Technology and Collaboration Technology pertaining to Collaboration Compounds which are existing as of the date of such Program termination under Article 12.

12.8 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 6 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) For purposes of clarity, the Parties understand and agree that, (i) unless the exclusivity obligations under Article 7 are expressly stated as binding upon a Party beyond the termination or expiration of this Agreement with respect to a Program or Collaboration Target, no such obligation(s) shall survive such termination or expiration; (ii) all Program Options for any Program(s) that is not terminated under Section 12.2 shall remain in effect in accordance with the terms of Article 4; and (iii) unless otherwise expressly stated, references in this Article 12 to "on a Collaboration Target-by-Collaboration Target basis" (and related references to "Collaboration Target" in such context) shall mean with respect to a Program that is directed to a particular Collaboration Target if such Program actually exists at the point that the relevant determination is made under Article 12, or with respect to all Collaboration Compounds and Licensed Products directed against a particular Collaboration Target, if the Program for such Collaboration Target has not yet commenced or if GSK has already exercised its Program Option for such Program at the point that the relevant determination is made under Article 12.

(c) The provisions of Sections 4.2.3, 4.2.7 and 4.3.2 (solely with respect to the effects of termination set forth therein in connection with Article 12), Articles 5 and 6 (in each case in accordance with the provisions of Article 12 or to the extent any payment payable hereunder is owed to a Party but unpaid as of the effective date of termination), Sections 6.9.3 and 6.10, Article 8 (with respect to (i) Jointly-Owned Collaboration Technology and (ii) any Know-How or Patent Rights Controlled by one Party but for which licenses granted to the other Party survive termination or expiration of this Agreement), and Articles 9, 11, 12, and 13 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 13

MISCELLANEOUS

13.1 Dispute Resolution by 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 Article 2 or Article 3 and which is not subject to the final decision-making authority of a Party under the provisions of Article 2 or Article 3, 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 [***] 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 13.1 shall not apply to alter or modify the indemnity obligations of the respective Parties under Article 11, 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.

13.2 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.

13.3 Assignment. This Agreement shall not be assignable by either Party to any Third Party or Parent 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 Parent 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) either Party may assign or transfer its rights to receive royalties and milestones under this Agreement (but no liabilities), without any consent of the other Party, to an Affiliate, to its Parent 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 Parent Company 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. 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.

13.4 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.

13.5 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*.

13.6 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, LLC
1896 Rutherford Road
Carlsbad, California 92008
Attention: President
Fax: 760-268-6868

with a copy to:
Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, California 92008
Attention: General Counsel
Fax: 760-268-4922

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: [***]

with a copy to: [***]

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.

13.7 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.

13.8 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.

13.9 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.

13.10 Entire Agreement. This Agreement, together with the Schedules and Exhibits hereto, the Side Agreement, the Convertible Promissory Note and the relevant applicable cited provisions of the JV Agreements, 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.

13.11 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.

13.12 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.

13.13 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 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.

13.14 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.

13.15 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. For clarity, the relevant applicable provisions of the JV Agreements shall not be construed under this paragraph.

13.16 Supremacy. In the event of any express conflict or inconsistency between this Agreement and the Initial Research Plan, any Research Plan or any Early Development Plan or of any Schedule or Exhibit hereto, the terms of this Agreement and of the Side Agreement shall control. The Parties understand and agree that the Schedules and Exhibits 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.

13.17 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.

13.18 Compliance with Laws: Each Party shall and shall ensure that its Affiliates, Parent Companies 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 LLC

By: /s/ Kleanthis G. Xanthopoulos, Ph.D.
Name: Kleanthis G. Xanthopoulos, Ph.D.
Title: President & CEO
Date: April 17, 2008

Glaxo Group Limited

By: /s/ Paul Williamson
Name: Paul Wiliamson
Title: For and on behalf of
Edinburgh Pharmaceutical Industries Limited
Corporate Director
Date: April 17, 2008

LIST OF SCHEDULES AND EXHIBITS

SCHEDULE 1.64 — Proposed Definition of Fully Absorbed Manufacturing Cost

SCHEDULE 1.103 – The miRNAs [***] as of the Effective Date

SCHEDULE 1.106 - The library of oligonucleotides [***] as of the Effective Date

SCHEDULE 6.8.2 – [***] Patent Rights Controlled by Regulus as of the Effective Date

SCHEDULE 8.10 – Parent Company Patents Controlled by Isis as of the Effective Date and covering [***] chemical modification

EXHIBIT A – Initial Research Plan

EXHIBIT B - Listing of Patent Rights Licensed to Regulus from its Parent Companies as of the Effective Date

EXHIBIT C - Listing of Patent Rights Assigned to Regulus from its Parent Companies or otherwise owned by Regulus as of the Effective Date

EXHIBIT D – Listing of Patent Rights Licensed to Regulus

EXHIBIT E – Initial Collaboration Targets

EXHIBIT F - Listing of Existing In-License Agreements

EXHIBIT G – Press Release

EXHIBIT H – Convertible Promissory Note

[***]

1

SCHEDULE 1.103

The miRNAs [***] as of the Effective Date (Release 10.1, December 2007)

[***]

1

SCHEDULE 1.106

The library of oligonucleotides [***] as of the Effective Date
(Release 10.1, December 2007)

[***]

1

SCHEDULE 6.8.2

[***] Patent Rights as of the Effective Date

[***]

1

SCHEDULE 8.10

Parent Company Patents Controlled by Isis as of the Effective Date
and covering [***] chemical modification

[***]

1

EXHIBIT A

Initial Research Plan

[***]

A-1

EXHIBIT B

Listing of Patent Rights Licensed to Regulus from its Parent Companies as of the Effective Date

[***]

B-1

EXHIBIT C

Listing of Patent Rights Assigned to Regulus from its Parent Companies or otherwise owned by Regulus as of the Effective Date

[***]

EXHIBIT D

Listing of Patent Rights Licensed to Regulus

[***]

EXHIBIT E

Initial Collaboration Targets

[***]

EXHIBIT F

Listing of Existing In-License Agreements

[***]

EXHIBIT G

Press Release

GlaxoSmithKline and Regulus Therapeutics Form Strategic Alliance To Develop MicroRNA Targeted Therapeutics to Treat Inflammatory Diseases

Companies Announce Significant microRNA Therapeutics Collaboration

LONDON & PHILADELPHIA & CARLSBAD, Calif., Apr 17, 2008 (BUSINESS WIRE) — GlaxoSmithKline (GSK) and Regulus Therapeutics LLC (Regulus) today announced a worldwide strategic alliance to discover, develop and market novel microRNA-targeted therapeutics to treat inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. Regulus is a joint venture between Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY) and Isis Pharmaceuticals, Inc. (Nasdaq: ISIS).

The alliance leverages Regulus' unique expertise and intellectual property position in the discovery and development of microRNA-targeted therapeutics and provides GSK with an option to license product 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 developed under each program by Regulus 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.

Regulus will receive $20 million in upfront payments from GSK, including a $15 million option fee and a $5 million note (guaranteed by Isis and Alnylam) that will convert into Regulus common stock in the future under certain specified circumstances. Regulus could also be eligible to receive up to $144.5 million in development, regulatory and sales milestone payments for each of the four microRNA-targeted therapeutics discovered and developed as part of the alliance. In addition to the potential of nearly $600 million Regulus could receive in option, license and milestone payments, Regulus would also receive tiered royalties up to double digits on worldwide sales of products resulting from the alliance.

"We are focused on finding innovative medicines through both internal efforts and by 'virtualizing' a portion of the inflammatory diseases pipeline. We are very excited to be working

with Regulus and exploring the therapeutic opportunities in inflammation offered by targeting microRNAs, an exciting new area of biology," said Jose Carlos Gutierrez-Ramos, Ph.D., Senior Vice President and head of the Immuno-Inflammation Center of Excellence for Drug Discovery of GSK. "When associated with an aberrant inflammatory response, microRNAs represent disease targets whose therapeutic modulation could revolutionize the way we treat immune diseases and provide benefits not readily achievable with today's medicines."

"GSK is an outstanding partner for Regulus, and we look forward to expanding our efforts in inflammation where a new class of therapeutics could offer novel options to treat disease," said Kleanthis G. Xanthopoulos, Ph.D., President and Chief Executive Officer of Regulus. "microRNA therapeutics represent an exciting new frontier for pharmaceutical research, opening many opportunities including those present in inflammation and immune diseases. As a leading

microRNA therapeutics company, Regulus has the expertise and access to proprietary antisense technologies, which provide the tools and potential to quickly move therapeutic programs toward the clinic. Through its relationship with Alnylam and Isis, Regulus also has a vast patent estate in microRNAs."

About microRNAs

microRNAs are a recently discovered class of genetically encoded small RNAs, approximately 20 nucleotides in length, and are believed to regulate the expression of a large number of human genes. microRNA therapeutics represent a new approach for the treatment of a wide range of human diseases. The inappropriate absence or presence of specific microRNAs in various cells has been shown to be associated with specific human diseases including cancer, viral infection, and metabolic disorders. Targeting microRNAs with novel therapeutic agents could result in high-impact and broadly acting treatments for human diseases.

About Regulus Therapeutics LLC

Regulus is a biopharmaceutical company formed to discover, develop and commercialize microRNA therapeutics. Regulus was founded in late 2007 as a joint venture between Alnylam Pharmaceuticals, a leader in RNAi therapeutics, and Isis Pharmaceuticals, a leader in antisense technologies and therapeutics. Isis and Alnylam scientists and collaborators were the first to discover microRNA antagonist strategies that work in vivo in animal studies (Krutzfeldt et al. Nature 438, 685-689 (2005); Esau et al. Cell Metab., 3, 87-98 (2006)). Isis and Alnylam have also created and consolidated key intellectual property for the development and commercialization of microRNA therapeutics. Regulus maintains facilities in Carlsbad, California. For more information, visit www.regulusrx.com.

About Alnylam Pharmaceuticals, Inc.

Alnylam is a biopharmaceutical company developing novel therapeutics based on RNA interference, or RNAi. The company is applying its therapeutic expertise in RNAi to address significant medical needs, many of which cannot effectively be addressed with small molecules or antibodies, the current major classes of drugs. Alnylam is leading the translation of RNAi as a new class of innovative medicines with peer-reviewed research efforts published in the world's top scientific journals including Nature, Nature Medicine, and Cell. The company is leveraging these capabilities to build a broad pipeline of RNAi therapeutics; its most advanced program is in Phase II human clinical trials for the treatment of respiratory syncytial virus (RSV) infection. In addition, the company is developing RNAi therapeutics for the treatment of influenza, hypercholesterolemia, and liver cancers, among other diseases. The company's leadership position in fundamental patents, technology, and know-how relating to RNAi has enabled it to form major alliances with leading companies including Medtronic, Novartis, Biogen Idec, and Roche. The company, founded in 2002, maintains headquarters in Cambridge, Massachusetts. For more information, visit www.alnylam.com.

About Isis Pharmaceuticals, Inc.

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 19 drugs in development. Isis' drug development programs are focused on treating cardiovascular and metabolic diseases. Isis' partners are developing antisense drugs invented by Isis to treat a wide variety of diseases. Ibis Biosciences, Inc., Isis' majority-owned subsidiary, is developing and commercializing the Ibis T5000(TM) Biosensor System, a revolutionary system to identify infectious organisms. Isis is a joint owner of Regulus Therapeutics LLC, a joint venture focused on the discovery, development and commercialization of microRNA therapeutics. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of over 1,500 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

Alnylam/Isis Forward Looking Statements

This press release includes forward-looking statements regarding the future therapeutic and commercial potential of Isis', Alnylam's and Regulus' business plans, technologies and intellectual property related to microRNA therapeutics being discovered and developed by Regulus, including statements regarding expectations around the newly formed relationship between Regulus and GSK. Any statement describing Isis', Alnylam's or Regulus' 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 its 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 Isis, Alnylam or Regulus, as the case may be. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis', Alnylam's and Regulus' programs are described in additional detail in Isis' annual report on Form 10-K for the year ended December 31, 2007 and in Alnylam's annual report on Form 10-K for the year ended December 31, 2007, which are on file with the SEC. Copies of this and other documents are available from Isis, Alnylam or Regulus.

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.

About the II CEDD

The Immuno-Inflammation Centre of Excellence for Drug Discovery is dedicated to discovering therapies for inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease and psoriasis. It is designed to integrate and better coordinate the progression of inflammatory disease medicines from

therapeutic hypothesis to clinical proof of concept. It focuses on building an innovative pipeline through both internal efforts and external alliances with other companies and research institutions and will focus on 'virtualizing' a portion of the inflammatory diseases pipeline by forming multiple risk-sharing/reward-sharing alliances.

EXHIBIT H

Convertible Promissory Note

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 [TBD], 2008
No.

FOR VALUE RECEIVED, Regulus Therapeutics LLC, a Delaware limited liability company (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 (i) [***] (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) "Collaboration Agreement" shall mean the Product Development and Commercialization Agreement by and between the Maker and Holder dated as of [ ].

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

(d) "Qualified Financing" shall mean the first issuance of [***] by the Maker to bona fide institutional investors, after the [***], 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).

(e) "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.

2. Conversion.

(a) 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), 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.

(b) Optional Conversion. In the event the Maker has been converted into, and remains, a [***], but has not closed a Qualified Financing within [***] of becoming a [***], the Holder may, with the consent of the Maker, convert some or all of the Outstanding Amount into shares of common stock of the Maker at a conversion price equal to then fair market value of the Maker's common stock, as agreed to by the Maker, Holder and each Guarantor. For purposes of

clarity, in the event the Maker, Holder and each Guarantor do not agree on the fair market value of the Maker's common stock, this Note will not be convertible pursuant to this Section 2(b).

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 Collaboration Agreement without cause or the Maker terminates the Collaboration 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 Collaboration Agreement by the Holder (or its assignee or successor under the Collaboration Agreement) by reason of breach of the Collaboration 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 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:
[***]

with a copy to:
[***]

if to Maker: Regulus Therapeutics LLC
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 LLC
By:
Title:

GUARANTORS:

ALNYLAM PHARMACEUTICALS, INC.
By:
Title:

ISIS PHARMACEUTICALS, INC.
By:
Title: .

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: August 7, 2008

/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: August 7, 2008

/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 June 30, 2008, 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: August 7, 2008

/s/ Stanley T. Crooke
Stanley T. Crooke, M.D., Ph.D.
Chief Executive Officer

/s/ B. Lynne Parshall
B. Lynne Parshall, J.D.
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.