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 September 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 November 3, 2008 was 97,002,050.

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)

	September 30, 2008 (Unaudited)	December 31, 2007
ASSETS		
Current assets:		
Cash and cash equivalents	$ 264,682	$ 138,614
Short-term investments	247,341	55,105
Contracts receivable	5,021	6,177
Inventories	5,511	2,817
Other current assets	6,988	4,604
Total current assets	529,543	207,317
Property, plant and equipment, net	14,019	7,131
Licenses, net	17,447	19,100
Patents, net	18,126	17,759

Deposits and other assets	5,557	7,551
Total assets	$ 584,692	$ 258,858
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 6,885	$ 4,507
Accrued compensation	3,956	10,461
Accrued liabilities	5,979	6,794
Derivative instrument related to Abbott's call option	1,069	—
Current portion of long-term obligations	—	7,238
Current portion of deferred contract revenue	99,794	33,205
Total current liabilities	117,683	62,205
$2^{5}/_{8}$% convertible subordinated notes	162,500	162,500
Long-term obligations, less current portion	5,478	362
Long-term deferred contract revenue	191,279	23,548
Total liabilities	476,940	248,615
Noncontrolling interest in Regulus Therapeutics LLC	6,315	9,371
Noncontrolling interest in Ibis Biosciences, Inc.	33,359	—
Stockholders' equity:		
Common stock, $0.001 par value; 200,000,000 shares authorized, 96,148,212 and 87,239,423 shares issued and outstanding at September 30, 2008 and December 31, 2007, respectively	96	87
Additional paid-in capital	900,303	827,992
Accumulated other comprehensive income	(1,271)	538
Accumulated deficit	(831,050)	(827,745)
Total stockholders' equity	68,078	872
Total liabilities, noncontrolling interest and stockholders' equity	$ 584,692	$ 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 September 30,		Nine Months Ended September 30,	
	2008	2007	2008	2007
Revenue:				
Research and development revenue under collaborative agreements	$ 31,240	$ 11,921	$ 78,739	$ 17,404
Licensing and royalty revenue	975	26,710	7,790	27,489
Total revenue	32,215	38,631	86,529	44,893
Expenses:				
Research and development	31,968	24,296	89,611	64,629
Selling, general and administrative	4,571	4,278	13,206	10,769
Total operating expenses	36,539	28,574	102,817	75,398
Income (loss) from operations	(4,324)	10,057	(16,288)	(30,505)
Other income (expense):				
Investment income	7,546	2,603	13,061	9,058
Interest expense	(1,509)	(1,488)	(4,297)	(6,132)
Gain on investments	—	—	—	3,510
Loss on early retirement of debt	—	—	—	(3,212)
Loss attributed to noncontrolling interest in Symphony GenIsis, Inc.	—	8,748	—	23,157
Loss attributed to noncontrolling interest in Regulus Therapeutics LLC	1,208	87	3,056	87
Loss attributed to noncontrolling interest in Ibis Biosciences, Inc.	267	—	1,163	—
Net income (loss)	3,188	20,007	(3,305)	(4,037)
Excess purchase price over carrying value of noncontrolling interest in Symphony GenIsis, Inc.	—	(125,311)	—	(125,311)
Net income (loss) applicable to common stock	$ 3,188	$ (105,304)	$ (3,305)	$ (129,348)
Basic and diluted net income (loss) per share	$ 0.03	$ (1.25)	$ (0.04)	$ (1.57)

Shares used in computing basic net income (loss) per share	95,863	83,942	93,786	82,650
Shares used in computing diluted net income (loss) per share	100,181	83,942	93,786	82,650

See accompanying notes.

Table of Contents

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

	Nine Months Ended September 30,	
	2008	2007
Net cash provided by (used in) operating activities	$ 231,207	$ (9,762)
Investing activities:		
Purchases of short-term investments	(305,998)	(61,052)
Proceeds from the sale of short-term investments	112,227	96,876
Purchases of property, plant and equipment	(7,050)	(1,452)
Acquisition of licenses and other assets	(2,585)	(2,407)
Proceeds from the sale of strategic investments	—	5,181
Acquisition of Symphony GenIsis, Inc.	—	(80,400)
Net cash used in investing activities	(203,406)	(43,254)
Financing activities:		
Net proceeds from issuance of equity	10,543	6,522
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	(7,238)	(5,657)
Proceeds from stock purchase by Genzyme Corporation, net of fees	49,962	—
Proceeds from capital contributions to Ibis Biosciences, Inc.	40,000	—
Proceeds from capital contribution to Regulus Therapeutics LLC	—	10,000
Net cash provided by financing activities	98,267	40,900
Net increase (decrease) in cash and cash equivalents	126,068	(12,116)
Cash and cash equivalents at beginning of period	138,614	114,514
Cash and cash equivalents at end of period	$ 264,682	102,398
Supplemental disclosures of cash flow information:		
Interest paid	$ 4,482	5,987
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 2,657	25
Common stock issued for Symphony GenIsis, Inc. acquisition	$ —	51,093

See accompanying notes.

Table of Contents

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

1. Basis of Presentation

The unaudited interim condensed consolidated financial statements for the three and nine month periods ended September 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 nine months of 2008 and 2007. During the first nine months 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 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 nine months of 2008 and 2007.

Table of Contents

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

	September 30, 2008	December 31, 2007
Raw materials	$ 5,151	$ 2,679
Work-in-process	360	138
	$ 5,511	$ 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 nine months of 2008 and 2007, we recorded a non-cash charge of $1.6 million and $515,000, 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.

Basic and diluted net income (loss) per share

We follow the provisions of SFAS 128, *Earnings per Share*. We compute basic net income (loss) per share by dividing the net income (loss) applicable to common stock by the weighted-average number of common shares outstanding during the period. We compute diluted net income (loss) per share using the weighted-average number of common shares and dilutive common equivalent shares outstanding during the period. Diluted common equivalent shares for the three months ended September 30, 2008 consisted of 3.3 million shares issuable upon exercise of stock options and 1.0 million shares issuable upon exercise of warrants. The calculation excludes the $2^{5}/_{8}$% convertible subordinated notes, the convertible promissory note to GlaxoSmithKline and 2.9 million stock options because the effect on diluted earnings per share would be anti-dilutive. As we incurred a loss for the three months ended September 30, 2007 and nine months ended September 30, 2008 and 2007, we did not include diluted common equivalent shares in the computation of diluted net loss per share because the effect would be anti-dilutive.

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 September 30, 2008, we had collaborative arrangements with nine entities that we consider to be variable interest entities under FIN 46R. For the first nine months of 2008, our condensed consolidated financial statements included two variable interest entities, Ibis and Regulus, for which we are the primary beneficiary. Until our acquisition of Symphony GenIsis in September 2007, our condensed consolidated financial statements for the first nine months of 2007 included two variable interest entities, Ibis and Symphony GenIsis, for which we were the primary beneficiary. Beginning in September 2007, our condensed consolidated financial statements also include the financial condition and results of operations of Regulus as we treat Regulus as a variable interest entity for which we are the primary beneficiary.

Table of Contents

Comprehensive income (loss)

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2008	2007	2008	2007
Comprehensive income (loss):				
Unrealized holding gains (losses)	$ (4,001)	$ 93	$ (1,809)	$ (620)
Reclassification adjustment for realized gains included in net loss	—	—	—	(3,147)
Net income (loss)	3,188	20,007	(3,305)	(4,037)
Comprehensive income (loss)	$ (813)	$ 20,100	$ (5,114)	$ (7,804)

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 on or after 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 nine months ended September 30, 2008 and 2007, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Nine Months Ended September 30,	
	2008	2007
Risk-free interest rate	3.1%	4.7%
Dividend yield	0.0%	0.0%
Volatility	55.1%	63.4%
Expected Life	4.6 years	4.6 years

Board of Director Stock Options:

	Nine Months Ended September 30,	
	2008	2007
Risk-free interest rate	3.8%	4.9%
Dividend yield	0.0%	0.0%
Volatility	62.2%	65.5%
Expected Life	7.6 years	7.4 years

ESPP:

	Nine Months Ended September 30,	
	2008	2007
Risk-free interest rate	2.8%	5.1%
Dividend yield	0.0%	0.0%
Volatility	61.4%	51.1%
Expected Life	6 months	6 months

Table of Contents

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 nine months ended September 30, 2008 and 2007 (in thousands, except per share data) was allocated as follows:

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2008	2007	2008	2007
Research and development	$ 3,105	$ 1,956	$ 9,372	$ 5,834
Selling, general and administrative	945	499	2,443	1,374
Non-cash compensation expense related to stock options	$ 4,050	$ 2,455	$ 11,815	$ 7,208

included in operating expenses				
Stock-based compensation expense, per share:				
Basic and diluted	$ (0.04)	$ (0.03)	$ (0.13)	$ (0.09)

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, $752,000 and $1.8 million of non-cash stock based compensation expense associated with these options for the three and nine months ended September 30, 2008 was included in our consolidated expenses compared to $80,000 for the same periods in 2007.

As of September 30, 2008, total unrecognized compensation cost related to non-vested stock-based compensation plans was $18.0 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 1.3 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, and 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 previously filed 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 standard states that entities with 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 standard is effective for fiscal years beginning on or after December 15, 2008, will be effective for our fiscal year 2009, and must be applied retrospectively to all periods presented. The adoption of FSP No. APB 14-1 will not impact our cash, cash equivalents and short-term investments but we anticipate that it will significantly increase the amount of interest expense that is recorded in our statement of operations due to the non-cash amortization of the debt discount. Additionally, we anticipate that the adoption of this standard will significantly decrease our debt balance as of December 31, 2008, with a corresponding increase to shareholders' equity.

Table of Contents

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, and will be effective for our fiscal year 2009. Early adoption for an existing instrument is not permitted. We do not expect this new guidance to have a material impact 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 September 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)	$ 482,543	$ 402,738	$ 79,805	$ —
Derivative instrument (2)	1,069	—	—	1,069(4)
Equity securities (3)	2,648	2,648	—	—
Total	$ 486,260	$ 405,386	$ 79,805	$ 1,069

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

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

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

(4) Represents the derivative instrument related to the call option granted to Abbott. As of September 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, Collaborative Arrangements and Licensing Agreements*).

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 September 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	(4,257)(2)
Exercise of subscription right	(50)(3)
Balance at September 30, 2008	$ 1,069

(1) Represents the derivative instruments related to the subscription right and call option granted to Abbott (see additional discussion in *Note 5, Collaborative Arrangements and Licensing Agreements*).

Table of Contents

(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 nine months 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, Collaborative Arrangements and Licensing Agreements*).

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 instruments that are 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, 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.

In 2007, 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 for a redemption price of $127.0 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 nine months of 2007, which included a $1.2 million non-cash write-off of unamortized debt issuance costs.

In December 2003, we obtained a $32.0 million term loan from Silicon Valley Bank. The term loan was payable in monthly payments of principal and interest and was to mature in December 2008. In September 2008, we paid off the remaining principal balance of $1.8 million plus accrued but unpaid interest.

5. Collaborative Arrangements and Licensing Agreements

The information discussed below represents partnerships we entered into during 2008 and any material changes to partnerships entered into prior to 2008. There are no other material changes 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 potential 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.

Table of Contents

Genzyme has agreed that it will not sell its equity investment in Isis stock that it 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 nine months ended September 30, 2008, we recognized revenue of $16.6 million and $31.6 million, respectively, related to the $100 million premium and the $175 million licensing fee, which represented 36% of our total revenue for the first nine months of 2008. Our Condensed Consolidated Balance Sheet at September 30, 2008 included deferred revenue of $243.4 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 Industries 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.

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 September 30, 2008 and December 31, 2007 included deferred revenue of $432,000 and $250,000, respectively, related to our agreements with ATL. For the three and nine months ended September 30, 2008, we recorded revenue of $0 and $1.4 million related to this collaboration, compared to $3,000 and $58,000 for the same periods in 2007. As of September 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 September 30, 2008 and December 31, 2007 included a short-term investment at fair market value of $1.7 million and $1.4 million, respectively, related to this equity investment.

OncoGenex Pharmaceuticals, formerly OncoGenex Technologies Inc.

In November 2001, we established a drug development collaboration with OncoGenex, a biotechnology company committed to the development of cancer therapeutics for patients with drug resistant and metastatic cancers, to co-develop and commercialize OGX-011, an anti-cancer antisense drug that targets clusterin. In July 2008, we amended and restated the original agreement and OncoGenex has elected to independently develop OGX-011. Under the amended agreement, OncoGenex is solely responsible for all future development activities, costs and partnering decisions related to OGX-011. We will receive single digit royalties on future revenues of OGX-011 and a portion of license fees and milestone payments received by OncoGenex from any future partner.

Table of Contents

In September 2003, the companies expanded their antisense drug development partnership to include the development of the second-generation antisense anti-cancer drug, OGX-225. OncoGenex is responsible for the preclinical and clinical development of the drug and we have no performance obligations. OncoGenex issued to us $750,000 of OncoGenex securities as payment for an upfront fee. In addition, OncoGenex will pay us milestone payments totaling up to $3.5 million for the achievement of clinical and regulatory milestones, and royalties on product sales. As of September 30, 2008, OncoGenex had not triggered any of the milestone payments related to OGX-225.

In January 2005, we further broadened our antisense drug development partnership with OncoGenex to allow for the development of two additional second-generation antisense anti-cancer drugs. Under the terms of the agreement, OncoGenex is responsible for the preclinical and clinical development of the drugs and we have no performance obligations. In April 2005, OncoGenex selected its first drug under this expansion, OGX-427 which targets Hsp27. OncoGenex paid us an upfront fee of $750,000 with a convertible note, which, in August 2005, converted into 244,300 shares of OncoGenex's preferred stock. OncoGenex will also pay us milestone payments totaling up to $5 million for the achievement of key clinical and regulatory milestones, and royalties on future product sales of these drugs. As of September 30, 2008, OncoGenex had not triggered any of the milestone payments related to OGX-427.

For the three and nine months ended September 30, 2008, we did not earn any revenue relating to our collaboration with OncoGenex, compared to $0 and $4,000 for the same periods in 2007. Our balance sheet at December 31, 2007 included an investment of $1.5 million related to our equity investment in OncoGenex. In August 2008, OncoGenex merged into Sonus Pharmaceuticals, a publicly traded company, and began doing business under the name OncoGenex Pharmaceuticals. Prior to finalizing the merger, OncoGenex effected a 1:18 reverse stock split. As a result of this merger, our equity investment in OncoGenex is now traded on a publicly traded exchange and at September 30, 2008 had a fair value of $227,000. The carrying value of our equity investment in OncoGenex has been negatively affected by the unusually poor conditions of the financial markets recently. As a result, we do not believe an impairment charge is appropriate at this time. As of September 30, 2008 and December 31, 2007, our ownership interest in OncoGenex was less than 10%.

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 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.

Table of Contents

The call option initially expires on December 31, 2008. 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 $1.2 million in the first nine months of 2008, until the balance becomes zero or until Abbott acquires Ibis. 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 $1.1 million represents the fair value of only the call option at September 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 a non-exclusive distributor for the marketing, promotion, solicitation, sales and distribution of Ibis assay kits and Ibis T5000 Biosensor Systems to customers worldwide. 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 GSK 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.

Table of Contents

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 nine months ended September 30, 2008, we recognized revenue of $681,000 and $1.4 million, respectively, compared to $41,000 for the same periods in 2007. The increase in 2008 is primarily due to the $15 million option fee received from GSK. Our Condensed Consolidated Balance Sheets at September 30, 2008 included deferred revenue of $14.1 million compared to $214,000 at December 31, 2007.

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 income (loss) from operations includes revenue less 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 its strategic alliance with GSK.

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

	Drug Discovery and Development	Ibis	Regulus	Total
Three Months Ended September 30, 2008				
Revenue:				
Research and development	$ 27,807	$ 2,128	$ 681	$ 30,616
Commercial revenue (1)	—	624	—	624
Licensing and royalty	975	—	—	975
Total segment revenue	$ 28,782	$ 2,752	$ 681	$ 32,215
Income (loss) from operations	$ 3,316	$ (5,430)	$ (2,210)	$ (4,324)
Three Months Ended September 30, 2007				
Revenue:				
Research and development	$ 7,242	$ 3,589	$ 41	$ 10,872
Commercial revenue (1)	—	1,049	—	1,049
Licensing and royalty	26,710	—	—	26,710
Total segment revenue	$ 33,952	$ 4,638	$ 41	$ 38,631
Income (loss) from operations	$ 11,393	$ (1,248)	$ (88)	$ 10,057
Nine Months Ended September 30, 2008				
Revenue:				
Research and development	$ 68,321	$ 6,072	$ 1,429	$ 75,822
Commercial revenue (1)	—	2,917	—	2,917
Licensing and royalty	7,790	—	—	7,790
Total segment revenue	$ 76,111	$ 8,989	$ 1,429	$ 86,529
Income (loss) from operations	$ 3,646	$ (14,743)	$ (5,191)	$ (16,288)
Total assets as of September 30, 2008	$ 523,381	$ 35,239	$ 26,072	$ 584,692
Nine Months Ended September 30, 2007				
Revenue:				
Research and development	$ 9,258	$ 5,615	$ 41	$ 14,914
Commercial revenue (1)	—	2,490	—	2,490

Licensing and royalty	27,489	—	—	27,489
Total segment revenue	$ 36,747	$ 8,105	$ 41	$ 44,893
Loss from operations	$ (23,165)	$ (7,252)	$ (88)	$ (30,505)
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 September 30,		Nine Months Ended September 30,	
	2008	2007	2008	2007
Partner A	52%	0%	36%	0%
Partner B	23%	13%	28%	11%
Partner C	10%	5%	11%	7%
Partner D	0%	69%	5%	59%

For the three months ended September 30, 2008 and 2007, we derived approximately 9% and 12%, respectively, of our revenue from agencies of the United States Government in aggregate, compared to 11% and 18% for the nine months ended September 30, 2008 and 2007, respectively. For the first nine months of 2008 and 2007, none of our significant partners were agencies of the United States Government.

Contract receivables from three significant partners comprised approximately 25%, 19% and 14% of contract receivables at September 30, 2008. Contract receivables from three significant partners comprised approximately 25%, 19% and 11% of contract receivables at December 31, 2007.

7. Subsequent Event

On October 15, 2008, we entered into a loan agreement related to an equipment financing. Under the loan agreement, we may borrow up to $10 million in principal to finance the purchase of equipment. Each loan under the loan agreement will have a term of approximately 3 years, with principal and interest payable monthly. Interest on amounts we borrow under the loan agreement will be calculated based upon the 3 year interest rate swap at the time each draw down is made plus 4%. We are using the equipment purchased under the loan agreement as collateral. In October 2008, we had drawn approximately $7.2 million in principal under this equipment financing.

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 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 30 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 $118 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 made a second $20 million investment to purchase additional equity in Ibis. 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. We plan to continue to add new drugs to grow our pipeline; already in 2008 we have added two drugs, PCSK9, our development candidate with BMS for which we earned a $2 million milestone payment and EXC001, a development candidate discovered by us and being developed by Excaliard Pharmaceuticals, Inc. for the local treatment of fibrosis.

Table of Contents

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 portfolio of drugs designed to treat a variety of health conditions. We currently have 19 drugs in development. Our partners are licensed to develop, with our support, 15 of these 19 drugs, which substantially reduces our development costs. We focus our internal drug development programs mainly on drugs to treat cardiovascular and metabolic 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 September 30, 2008, we had earned $75.1 million in revenue under our government contracts and grants, and we have an additional $9.9 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 initiated a Phase 3 mipomersen study in heterozygous Familial Hypercholesterolemia (FH) subjects with coronary artery disease.
- We completed enrollment of the pivotal Phase 3 mipomersen study in homozygous FH subjects.
- We were granted broad patent coverage for the therapeutic use of antisense compounds targeting apolipoprotein B, U.S. Patent No. 7,407,943 entitled "Antisense modulation of apolipoprotein B expression".
- We initiated a Phase 1 study of ISIS 353512, an antisense drug that targets C-reactive protein.

Table of Contents

Other Drug Programs

- ATL and Teva reported encouraging Phase 2 results for ATL/TV1102 at the World Congress on Treatment and Research in Multiple Sclerosis.
- Atlantic Healthcare received U.S. orphan drug designation for alicaforsen for the treatment of pouchitis.
- Excaliard selected a development compound, EXC001, for the local treatment of fibrosis and scarring.
- iCo Therapeutics Inc. reported interim data from an ongoing Phase 1 study of iCo-007 in patients with diffuse diabetic macular edema that showed that iCo-007 appears to be well tolerated.
- OncoGenex was granted Fast Track Designation from the U.S. Food & Drug Administration for OGX-011 in combination with docetaxel for progressive metastatic prostate cancer.
- OncoGenex reached an agreement with the FDA on the design of a Phase 3 registration trial of OGX-011 in patients with hormone refractory prostate cancer, via the Special Protocol Assessment process.

Ibis Biosciences

- Ibis received an additional $20 million investment from Abbott in June 2008 for a total investment of $40 million and 18.6 percent equity in Ibis, retaining Abbott's exclusive option to purchase the remaining equity in Ibis.
- To date, in 2008, Ibis was awarded up to $11.6M in government grants and contracts to fund the expansion of applications of the Ibis technology.
- Ibis presented seven research studies highlighting the power of the Ibis T5000 to rapidly and accurately detect and characterize pathogens at the International Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and the Annual Infectious Disease Society of America.
- Ibis provided the development plan for the next-generation instrument platform, which will build upon Ibis' current technology and be tailored for use in a clinical diagnostic setting.

Regulus Therapeutics (microRNA Joint Venture)

- Regulus published research in Molecular and Cellular Biology demonstrating that the microRNA, miR-21, plays a key role in the regulation of certain cancer cells, including an aggressive form of brain cancer.
- Regulus published research in Cancer Cell showing that the microRNA, miR-296, is involved in promoting the formation of new blood vessels in cancer cells.
- Regulus added Stelios Papadopoulos to its Board of Directors and appointed Garry Menzel as Executive Vice President.

Additional Highlights

- We were granted patents that significantly expand the scope of Isis' "Crooke" patent estate. U.S. Patent No. 7,432,250 and U.S. Patent No. 7,432,249 add broad claims that cover RNA-based product compositions and methods of treatment.

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.

Table of Contents

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.

Results of Operations

Revenue

Total revenue for the three and nine months ended September 30, 2008 was $32.2 million and $86.5 million, respectively, compared to $38.6 million and $44.9 million for the same periods in 2007. The significant increase in 2008 year to date revenue over 2007 was a result of our 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.

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. For example, in the third quarter of 2007, we earned $26.5 million of licensing revenue from Alnylam’s sublicense of our technology for the development of RNA interference therapeutics to Roche.

Table of Contents

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2008	2007	2008	2007
Drug Discovery and Development:				
Research and development revenue	$ 27,807	$ 7,242	$ 68,321	$ 9,258
Licensing and royalty revenue	975	26,710	7,790	27,489
	$ 28,782	$ 33,952	$ 76,111	$ 36,747
Ibis Biosciences:				
Research and development revenue	$ 2,128	$ 3,589	$ 6,072	$ 5,615
Commercial revenue (1)	624	1,049	2,917	2,490
	$ 2,752	$ 4,638	$ 8,989	$ 8,105
Regulus Therapeutics:				
Research and development revenue	$ 681	$ 41	$ 1,429	$ 41
	$ 681	$ 41	$ 1,429	$ 41
Total Revenue:				
Research and development revenue	$ 30,616	$ 10,872	$ 75,822	$ 14,914
Commercial revenue (1)	624	1,049	2,917	2,490
Licensing and royalty revenue	975	26,710	7,790	27,489
	$ 32,215	$ 38,631	$ 86,529	$ 44,893

(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 nine months ended September 30, 2008 was $27.8 million and $68.3 million, respectively, compared to $7.2 million and $9.3 million for the same periods in 2007. The increase was 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 nine months ended September 30, 2008 was $975,000 and $7.8 million, respectively, compared to $26.7 million and $27.5 million for the same periods in 2007. Licensing and royalty revenue in 2007 was higher primarily due to the $26.5 million licensing revenue that we earned from Alnylam in the third quarter of 2007.

Ibis Biosciences, Inc.

Ibis' revenue for the three and nine months ended September 30, 2008 was $2.8 million and $9.0 million, respectively, compared to $4.6 million and $8.1 million for the same periods in 2007. The increase in Ibis' year to date 2008 revenue compared to the same period in 2007 was primarily a result of the government contracts awarded in late 2007 and 2008 and the increased number of Ibis' T5000 Biosensor System placements. So far in 2008, Ibis has been awarded up to $11.6 million of new contracts that support Ibis' continued revenue growth by expanding the applications for the T5000 Biosensor System. The decrease in revenue in the third quarter of 2008 compared to the same period in 2007 was primarily due to additional revenue that was recorded in the third quarter of 2007 resulting from a one-time favorable adjustment in our government contract rates. Ibis' revenue in 2008 included revenue from the distribution agreement Ibis and Abbott entered into in March 2008. 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.

From inception through September 30, 2008, Ibis has earned $75.1 million in revenue from various government agencies to further the development of our Ibis T5000 Biosensor System and related assay kits. An additional $9.9 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.

Table of Contents

Regulus Therapeutics

Regulus' revenue for the three and nine months ended September 30, 2008 was $681,000 and $1.4 million respectively, compared to $41,000 for the same periods in 2007. The increase was primarily due to revenue from its collaboration with GSK. As part of Regulus' strategic alliance with GSK, Regulus received a $15 million upfront fee, which Regulus 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.

Operating Expenses

Operating expenses for the three and nine months ended September 30, 2008 were $36.5 million and $102.8 million, respectively, compared to $28.6 million and $75.4 million for the same periods of 2007. Although operating expenses have increased in 2008 compared to 2007, our operating expenses in the third quarter of 2008 were essentially flat compared to operating expenses in the second quarter of 2008.

The higher year to date expenses in 2008 compared to 2007 were primarily due to increased activity levels related to our planned investment to fill our pipeline and the expansion of our clinical development programs, including increased expenses for manufacturing of drug supplies for our corporate partners and our internal drug development programs. Additionally, Ibis' operating expenses have increased by $8.2 million, excluding non-cash compensation expense related to stock options, in the first nine months of 2008 compared to the same period in 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 nine months of 2008 compared to the same period in 2007 was an increase of $4.5 million, excluding non-cash compensation expense related to stock options, in expenses associated with our joint venture, Regulus.

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 $4.1 million and $11.8 million for the three and nine months ended September 30, 2008 compared to $2.5 million and $7.2 million for the same periods in 2007, primarily reflecting the increase in our stock price from the first nine months of 2007 to the first nine months of 2008.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2008	2007	2008	2007
Drug Discovery and Development	$ 22,739	$ 20,581	$ 64,148	$ 53,996
Ibis Biosciences	7,743	5,489	22,351	14,145
Regulus Therapeutics	2,007	49	4,503	49
Non-cash compensation expense related to stock options	4,050	2,455	11,815	7,208
Total operating expenses	$ 36,539	$ 28,574	$ 102,817	$ 75,398

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 related to stock options 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 September 30,		Nine Months Ended September 30,	
	2008	2007	2008	2007
Research and development expenses	$ 28,863	$ 22,340	$ 80,239	$ 58,795
Non-cash compensation expense related to stock options	3,105	1,956	9,372	5,834
Total research and development expenses	$ 31,968	$ 24,296	$ 89,611	$ 64,629

Table of Contents

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

	Three Months Ended September 30,		Six Months Ended September 30,	
	2008	2007	2008	2007
Drug Discovery and Development	$ 20,841	$ 18,014	$ 58,801	$ 47,626
Ibis Biosciences	6,207	4,278	17,545	11,121
Regulus Therapeutics	1,815	48	3,893	48
Non-cash compensation expense related to stock options	3,105	1,956	9,372	5,834
Total research and development expenses	$ 31,968	$ 24,296	$ 89,611	$ 64,629

For the three and nine months ended September 30, 2008, we incurred total research and development expenses, excluding non-cash compensation expense, of $28.9 million and $80.2 million, respectively, compared to $22.3 million and $58.8 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.

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 nine months ended September 30, 2008 were $4.6 million and $13.4 million, respectively, compared to $3.6 million and $10.1 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 September 30,		Nine Months Ended September 30,	
	2008	2007	2008	2007
Mipomersen	$ 2,611	$ 3,165	$ 9,193	$ 7,387
Other antisense development projects	3,417	3,402	10,206	9,059
Development overhead costs	910	1,850	2,657	4,177
Non-cash compensation expense related to stock options	818	693	2,596	2,033
Total antisense drug development	$ 7,756	$ 9,110	$ 24,652	$ 22,656

Table of Contents

Antisense drug development expenditures of $6.9 million and $22.1 million, excluding non-cash compensation expense related to stock options, for the three and nine months ended September 30, 2008 compared to $8.4 million and $20.6 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 $910,000 and $2.7 million for the three and nine months ended September 30, 2008, compared to $1.9 and $4.2 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 clinical research programs that fuel our Phase 3 pipeline. When our products are in Phase 1 or Phase 2 clinical trials, they are in a dynamic state where we continually adjust the development strategy for each product. Although we may characterize a product as "in Phase 1" or "in Phase 2," it does not mean that we are conducting a single, well-defined study with dedicated resources. Instead, we allocate our internal resources on a shared basis across numerous products based on each product's particular needs at that time. This means we are constantly shifting resources among products. Therefore, what we spend on each product during a particular period is usually a function of what is required to keep the products progressing in clinical development, not what products we think are most important. For example, the number of people required to start a new study is large, the number of people required to keep a study going is modest and the number of people required to finish a study is large. However, such fluctuations are not indicative of a shift in our emphasis from one product to another and cannot be used to accurately predict future costs for each product. And, because we always have numerous products in preclinical and early stage clinical research, the fluctuations in expenses from product to product, in large part, offset one another. If we partner a drug, it may affect the size of a trial, its timing, its total cost and the timing of the related cost. Our partners are developing, with our support, 15 of our 19 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. 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. Manufacturing and operations expenses, excluding non-cash compensation expense, for the three and nine months ended September 30, 2008 were $3.3 million and $8.7 million, respectively, compared to $2.1 million and $5.0 million for the same periods in 2007. The increase was primarily due to the costs associated with the manufacturing of drug supplies for our corporate partners and our internal drug development programs.

Table of Contents

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 September 30,		Nine Months Ended September 30,	
	2008	2007	2008	2007
Personnel costs	$ 2,678	$ 1,602	$ 5,545	$ 4,606
Occupancy	1,814	1,546	4,911	4,524
Depreciation and amortization	1,961	1,193	4,645	3,584
Insurance	227	227	680	715
Other	(98)	305	938	1,219
Non-cash compensation expense related to stock options	561	188	1,776	558
Total R&D support costs	$ 7,143	$ 5,061	$ 18,495	$ 15,206

R&D support costs, excluding non-cash compensation expense related to stock options, for the three and nine months ended September 30, 2008 were $6.6 million and $16.7 million, respectively, compared to $4.9 million and $14.6 million for the same periods in 2007. The increase in the first nine months of 2008 compared to the first nine months of 2007 was 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 September 30,		Nine Months Ended September 30,	
	2008	2007	2008	2007
Drug Discovery and Development	$ 6,010	$ 4,272	$ 14,695	$ 12,648
Ibis Biosciences	572	601	2,024	2,000
Non-cash compensation expense related to stock options	561	188	1,776	558
Total R&D support costs	$ 7,143	$ 5,061	$ 18,495	$ 15,206

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 September 30,		Nine Months Ended September 30,	
	2008	2007	2008	2007
Selling, general and administrative expenses	$ 3,626	$ 3,779	$ 10,763	$ 9,395
Non-cash compensation expense related to stock options	945	499	2,443	1,374
Total selling, general and administrative expenses	$ 4,571	$ 4,278	$ 13,206	$ 10,769

Table of Contents

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2008	2007	2008	2007
Drug Discovery and Development	$ 1,898	$ 2,566	$ 5,347	$ 6,370
Ibis Biosciences	1,536	1,212	4,806	3,024
Regulus Therapeutics	192	1	610	1
Non-cash compensation expense related to stock options	945	499	2,443	1,374
Total selling, general and administrative expenses	$ 4,571	$ 4,278	$ 13,206	$ 10,769

Selling, general and administrative expenses, excluding non-cash compensation expense related to stock options, for the three and nine months ended September 30, 2008 were $3.6 million and $10.8 million, respectively, compared to $3.8 million and $9.4 million for the same periods in 2007. The increase was 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 commercial revenue for its commercial activities, research and development expenses and selling, general and administrative expenses. Ibis' research and development expenses are 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' research and development expenses include 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 also 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 personnel and 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 September 30,		Nine Months Ended September 30,	
	2008	2007	2008	2007
Cost of commercial revenue	$ 203	$ 767	$ 1,751	$ 2,004
Research and development expenses	6,004	3,510	15,794	9,117
Selling, general and administrative expenses	1,536	1,212	4,806	3,024
Non-cash compensation expense related to stock options	439	397	1,381	1,212
Total Ibis operating expenses	$ 8,182	$ 5,886	$ 23,732	$ 15,357

Ibis' operating expenses, excluding non-cash compensation expense related to stock options, were $7.7 million and $22.4 million for the three and nine months ended September 30, 2008, compared to $5.5 million and $14.1 million for the same periods in 2007, respectively. The increase in operating expenses primarily reflected 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 expenses for Ibis to increase as we continue to expand this business.

Table of Contents

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 $3.1 million and $87,000 for the first nine months of 2008 and 2007, respectively, 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. 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 its GSK collaboration.

Investment Income

Investment income for the three and nine months ended September 30, 2008 totaled $7.5 million and $13.1 million, respectively, compared to $2.6 million and $9.1 million for the same periods in 2007. Included in investment income for 2008 are non-cash adjustments related to the value of the call option and subscription right that we granted to Abbott. The non-cash adjustments increased investment income by $4.1 million and $4.3 million for the three and nine months ended September 30, 2008, respectively. Excluding these non-cash adjustments, interest income would have been $3.4 million and $8.8 million for the three and nine months ended September 30, 2008. Although we have a significantly higher average cash balance in 2008 because we received $325 million from Genzyme, $40.5 million from Abbott and $20 million from GSK, we anticipate interest income, without non-cash adjustments, to only be moderately higher in future quarters due to the current conditions in the financial markets.

Interest Expense

Interest expense for the three and nine months ended September 30, 2008 totaled $1.5 million and $4.3 million, respectively, compared to $1.5 million and $6.1 million for the same periods in 2007. The decrease in year to date interest expense was due to the effect of a lower average debt balance in the first nine months of 2008 compared to the first nine months of 2007 primarily related to the fact that a portion of our old 5$^{1}/_{2}$% notes was outstanding until we repaid the remaining balance in May 2007.

In 2009, when we adopt the new convertible debt accounting standard, FSP No. APB 14-1, we anticipate that the amount of interest expense that is recorded in our statement of operations will increase due to the non-cash amortization of the debt discount. For additional information about FSP No. APB 14-1, see *Note 2, Significant Accounting Policies*, in the Notes to Condensed Consolidated Financial Statements.

Gain on Investments

Gain on investments for the first nine months ended September 30, 2007 was $3.5 million, 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 nine months of 2008.

Loss on Early Retirement of Debt

Loss on early retirement of debt for the first nine months ended September 30, 2007 was $3.2 million, reflecting the early extinguishment of our 5$^{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 nine months of 2008.

Net Income (Loss)

Net income for the three months ended September 30, 2008 was $3.2 million and net loss for the nine months ended September 30, 2008 was $3.3 million, respectively, compared to net income of $20.0 million and net loss of $4.0 million for the same periods in 2007. Our net loss for the first nine months of 2008 was lower than the first nine months of 2007 primarily due to a decrease in our loss from operations offset by the $23.2 million benefit that we recognized for nine months ended September 30, 2007 in the loss attributed to noncontrolling interest in Symphony GenIsis, Inc., resulting from our collaboration with Symphony GenIsis. We did not record this benefit in 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.

Table of Contents

Net Income (Loss) Applicable to Common Stock

Net income applicable to common stock for the three months ended September 30, 2008 was $3.2 million and net loss applicable to common stock for the nine months ended September 30, 2008 was $3.3 million, compared to net loss applicable to common stock of $105.3 million and $129.3 million for the same periods in 2007. In the third quarter of 2007, we purchased the equity of Symphony GenIsis. The $125.3 million on our Condensed Consolidated Statement of Operations in the line item called Excess Purchase Price over Carrying Value of Noncontrolling Interest in Symphony GenIsis, Inc. represents a deemed dividend paid to the previous owners of Symphony GenIsis. This deemed dividend only impacts our net loss applicable to common stock and our net loss per share calculations for the three and nine months ended September 30, 2007 and does not affect our net income (loss).

Net Income (Loss) Per Share

Basic and diluted net income per share for the three months ended September 30, 2008 was $0.03 per share. Basic and diluted net loss per share for the nine months ended September 30, 2008 was $0.04 per share, compared to $1.25 per share and $1.57 per share for the three and nine months ended September 30, 2007. The decrease in net loss per share for the first nine months of 2008 compared to the first nine months 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 September 30, 2008, we have earned approximately $663.8 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 September 30, 2008, we have raised net proceeds of approximately $800.7 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.

At September 30, 2008, we had cash, cash equivalents and short-term investments of $512.0 million and stockholders' equity of $68.1 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 September 30, 2008, we had consolidated working capital of $411.9 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 September 30, 2008, our debt and other long-term obligations totaled $168.0 million, compared to $170.1 million at December 31, 2007. The decrease in our debt and other obligations was due to the full payment of the Silicon Valley Bank term loan in September 2008 partly offset by the $5 million convertible promissory note Regulus issued to GSK. In October 2008, we also financed $7.2 million in capital additions under an equipment financing arrangement. This equipment financing arrangement allows us to borrow up to $10 million in principal to finance the purchase of equipment. We expect to use the remaining amount available under this arrangement over time to fund capital equipment acquisitions required to support our business. We will continue to use equipment financing as long as the terms remain commercially attractive.

Based on our existing and committed cash, not including the cash we could receive from Abbott if Abbott completes its purchase of Ibis, we remain on track to meet our cash guidance with a 2008 year end cash balance greater than $450 million, which is sufficient to fund our activities for at least five years.

Table of Contents

The following table summarizes our contractual obligations as of September 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, including accrued interest	$ 5.1	$ —	$ 5.1	$ —	$ —
Other Obligations	$ 0.4	$ —	$ —	$ —	$ 0.4
Operating Leases	$ 22.9	$ 3.5	$ 5.8	$ 3.9	$ 9.7

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

In December 2003, we obtained a $32.0 million term loan from Silicon Valley Bank which was to mature in December 2008. The term loan was payable in monthly payments of principal and interest and bore 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. The loan was secured by substantially all of our operating assets, excluding intellectual property, real estate, and certain equity investments. In September 2008, we paid off the remaining principal balance of $1.8 million plus accrued but unpaid interest.

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, in 2007 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 September 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.

In addition to contractual obligations, we had outstanding purchase orders as of September 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.

Primarily as a result of the significant upfront funding that we received from our strategic alliance with Genzyme in 2008, we anticipate having significant taxable income in 2009. To minimize our federal income tax liability, we plan to use our net operating loss carryforwards to offset a majority of our taxable income, subject to the completion of our Section 382 analysis. For our California taxes, the recent tax law changes that were enacted with the 2008/2009 California Budget have suspended the use of net operating loss carryforwards in 2008 and 2009. We intend to offset our California income tax liability to the full extent allowed under the tax regulations with our research and development tax credits, which is limited to 50 percent. As a result, we anticipate having a large tax liability in 2009, which will require us to make an estimated tax payment in December 2009.

Table of Contents

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 September 30, 2008, we had accumulated losses of approximately $831.1 million and stockholders' equity of approximately $68.1 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, Bristol-Myers Squibb Company, iCo Therapeutics Inc., Eli Lilly and Company, Merck & Co., Inc., OncoGenex Technologies Inc., Ortho-McNeil, Inc. and Teva Pharmaceutical Industries Ltd. 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.

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;

Table of Contents

- 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.

For example, in October 2008, Sequenom, Inc. filed a complaint in the U.S. District Court in Delaware alleging patent infringement by Ibis.

As a further 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.

Table of Contents

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 cash we could receive from Abbott if Abbott completes its purchase of Ibis, we remain on track to meet our cash guidance with a 2008 year end cash balance greater than $450 million, which we expect 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.

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.

Table of Contents

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 September 30, 2008, the market price of our common stock ranged from $10.91 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.

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.

Table of Contents

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.

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.

Table of Contents

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;
- 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.

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:

Table of Contents

- 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 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.

Table of Contents

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 nine months ended September 30, 2008 and 2007, we derived approximately 11% and 18%, 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.

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.

Table of Contents

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
- 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.

Table of Contents

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 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.

Table of Contents

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

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.

Table of Contents

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 is being pursued in Massachusetts Superior Court.

On October 31, 2008, Ibis received a copy of a complaint filed by Sequenom, Inc. in the U.S. District Court in Delaware. The Sequenom complaint alleges patent infringement by Ibis. We are evaluating the complaint.

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

Not applicable

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable

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

Not applicable

ITEM 5. OTHER INFORMATION

Not applicable

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.1	Amended and Restated License Agreement dated July 2, 2008 between the Registrant and OncoGenex Technologies Inc. (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)	November 10, 2008
/s/ B. Lynne Parshall B. Lynne Parshall, J.D.	Director, Chief Operating Officer, Chief Financial Officer and Secretary (Principal financial and accounting officer)	November 10, 2008

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

EXECUTION VERSION

AMENDED AND RESTATED LICENSE AGREEMENT

THIS AMENDED AND RESTATED LICENSE AGREEMENT ("Agreement") is made and entered into effective as of July 2, 2008 (the "Amendment Effective Date"), by and between ONCOGENEX TECHNOLOGIES INC., having offices at #400 – 1001 West Broadway, Vancouver, B.C. V6H 4B1 ("OncoGenex") and ISIS PHARMACEUTICALS, INC., having principal offices at 1896 Rutherford Road, Carlsbad CA 92008-7208 ("Isis"). OncoGenex and Isis each may be referred to herein individually as a "Party," or collectively as the "Parties."

WHEREAS, the Parties entered into a Collaboration and Co-Development Agreement dated November 16, 2001 (the "Original Collaboration Agreement") which collaboration resulted in the development of OGX-011, a second generation antisense inhibitor of Clusterin;

AND WHEREAS, the Parties now wish for OncoGenex to proceed with unilateral development of OGX-011 and Products and in this connection wish to enter into this Agreement to amend and restate the Original Collaboration Agreement, as provided herein.

NOW, THEREFORE, the Parties do hereby agree as follows:

ARTICLE 1
DEFINITIONS

Capitalized terms used in this Agreement and not otherwise defined herein have the meanings set forth in Appendix A.

ARTICLE 2
TERMINATION OF COLLABORATION

Section 2.1 **Previous Collaboration.** Pursuant to the Original Collaboration Agreement, commencing November 16, 2001 the Parties collaborated to jointly develop OGX-011 and the Products to the present stage of development (the "Collaboration"). As of the Amendment Effective Date, the Collaboration is terminated.

ARTICLE 3
CESSATION OF OPERATION OF COLLABORATION

Section 3.1 **Dissolution of Operating Committee.** Pursuant to Article 3 of the Original Collaboration Agreement, the Parties established an "Operating Committee" to oversee the Collaboration. As of the Amendment Effective Date, the Operating Committee is hereby dissolved and the Operating Committee will have no further responsibility, authority or function.

*Certain information in this exhibit has been omitted as confidential, as indicated by [***]. This information has been filed separately with the Commission.

ARTICLE 4
LICENSE GRANT, TECHNOLOGY TRANSFER, DILIGENCE

Section 4.1 **License Grant.**

4.1.1 **Nonexclusive License.** Subject to the terms and conditions of this Agreement, Isis hereby grants to OncoGenex a worldwide, nonexclusive license, with the right to grant sublicenses as set forth in Section 4.1.2 below, under the Isis Core Technology, Isis Core Technology Patents, Isis Manufacturing Technology and Isis Manufacturing Patents to research, develop, make, have made, use, gain regulatory approval, commercialize, sell, offer for sale, have sold, export and import OGX-011 and Products for all uses.

4.1.2 **Sublicenses.** The licenses granted to OncoGenex under this Article 4 are sublicensable only in connection with a license of OGX-011 or a Product to any Affiliate of OncoGenex or to any Third Party, in each case for the continued Development and Commercialization of OGX-011 or such Product in accordance with the terms of this Agreement, *provided* that (i) such Affiliate or Third Party will agree in writing to be bound by and subject to all applicable terms and conditions of this Agreement in the same manner and to the same extent as OncoGenex, and (ii) OncoGenex will remain responsible for the performance of this Agreement and will cause such Affiliate or Third Party to comply with the applicable terms and conditions of this Agreement. In addition to the requirements and limitations set forth above, with respect to the Isis Manufacturing Technology, OncoGenex will (a) name Isis as a third party beneficiary with the right to directly enforce Article 7 (Confidentiality) of this Agreement against such Affiliate or Third Party, (b) promptly notify Isis in writing specifically identifying the Isis Manufacturing Technology to be disclosed to such Third Party and identifying by name such Third Party and (c) use appropriate precautions and include provisions in such sublicense to protect the Isis Manufacturing Technology such that the sublicensee will not use any Isis Manufacturing Technology to manufacture any other ASOs for Third Parties and in any event OncoGenex will not provide to any Third Party manufacturer any batch record transferred by Isis to OncoGenex under this Agreement.

4.1.3 **Follow On/Back-up Compounds.** At OncoGenex' request, Isis and OncoGenex will negotiate in good faith a reasonable research plan and corresponding budget, at the same FTE rate as set forth in the Original Collaboration Agreement, to identify exclusively for OncoGenex additional MOE Gapmers that modulate Clusterin ("Follow-on Compounds"). In such event and after OncoGenex has paid Isis pursuant to such research plan, the definition of "Product" under this Agreement shall include the Follow-on Compounds.

4.1.4 **Improvements**. To the extent that Isis has the right to license an Improvement, the Parties will negotiate in good faith regarding the use of any such Improvement to research, develop, make, have made, use, gain regulatory approval, commercialize, sell, offer for sale, have sold, export and import OGX-011 and Products for all uses. If OncoGenex gives to Isis written notice of its desire to obtain a license to an Improvement, the Parties shall negotiate in

good faith and attempt to reach mutual agreement upon a commercially reasonable agreement under which OncoGenex obtains a license under such Improvement, and all patent and other intellectual property rights therein and thereto, to research, develop, make, have made, use, sell, offer for sale, have sold and import Products. The license will be sublicensable in accordance

with Section 4.1.2. If requested by OncoGenex, Isis will give to OncoGenex a written description of such Improvement in reasonably specific detail, together with such data and information as reasonably requested by OncoGenex.

4.1.5 Exclusivity. Subject to Section 12.2.2, neither Isis nor any of its Affiliates will (a) engage, on behalf of itself or for any other party, in the research, development, manufacture, production, release or commercialization of ASOs that act predominantly by [***] Clusterin [***] or that are [***] Clusterin [***] or products containing such ASOs, or (b) grant to any other party any license, immunity or other right, in each case other than a Permitted License or as otherwise set forth on Appendix F, to do any of the foregoing. Isis represents and warrants that all Permitted Licenses as of the Amendment Effective Date are listed on Appendix F.

4.1.6 [***] and [***] Patents. Without limiting OncoGenex' obligations under Section 6.2.4, Isis will timely pay in full all amounts required to be paid by Isis, and timely perform in full all obligations required to be performed by Isis, under the [***] Agreement and the [***] Agreement. Without the prior express written consent of OncoGenex (such consent not to be unreasonably withheld, conditioned or delayed), Isis will not (and will take no action or make no omission to) modify or waive any material provision of the [***] Agreement or the [***] Agreement that could impair the value of the sublicenses granted to OncoGenex under the [***] Agreement or the [***] Agreement, or to terminate or have terminated the [***] Agreement or the [***] Agreement.

Section 4.2 **Assignment, Technology Transfer.**

4.2.1 Assignment. Isis previously has assigned and transferred, or will assign and transfer, and hereby does assign and transfer, to OncoGenex or its designee, all rights, title, and interests in and to the Product-Specific Technology and the Product-Specific Technology Patents. Simultaneously with the execution of this Agreement, Isis will execute and deliver a confirmatory assignment relating to all Product-Specific Technology Patents listed on Appendix G.

4.2.2 Isis Transfer of Technology. Subject to the terms and conditions of this Agreement, Isis will transfer to OncoGenex, or a Third Party designate selected solely by OncoGenex, (a) all know-how required to use and interpret the Release Methods, (b) all software necessary for the conduct of the Release Methods, (c) the Supply Chain Network necessary for the manufacture of the Product, (d) any Isis Core Technology, (e) any Product-Specific Technology and (f) the Isis Manufacturing Technology, in each case Controlled by Isis on the Amendment Effective Date. Isis will use Commercially Reasonable Efforts to complete such transfer pursuant to this Section 4.2.1 within 120 days following the Amendment Effective Date. If (i) such transfer requires more than [***] (ii) such transfer is made to a Third Party manufacturer, or (iii) OncoGenex reasonably requests further technical assistance with respect thereto, then, in each case, OncoGenex will pay to Isis the standard Isis FTE rate for the time to complete such transfer or to provide such assistance. Any transfer made under this Section 4.2.1 is subject to Section 4.1.2 and Article 7.

4.2.3 Transfer of Records. Isis will provide to OncoGenex promptly following OncoGenex' written request, (a) all batch records related to any Product, including but not

limited to corresponding release data, (b) toxicity and pharmacokinetic data and reports related to such Product, (c) pharmacology data and reports related to such Product, (d) Product and OGX-011 characterization data, (e) Product and OGX-011 stability data, (f) any other records, including, but not limited to, raw data or interim or final reports, related to such Product or OGX-011, and (g) all Regulatory Documents, in each case that are in the possession of Isis or its Affiliates, or any third party engaged by Isis or any of its Affiliates. OncoGenex will promptly share with Isis a summary of the data and results related to each clinical trial conducted by OncoGenex that was completed or commenced prior to the Amendment Effective Date in substantially the form, and with substantially the content, of OncoGenex' regular reports provided to its board of directors regarding such clinical trial, but in any event by the later of (i) 60 days following the Amendment Effective Date and (ii) the date OncoGenex comes into possession of such information.

Section 4.3 Supply of Existing OGX-011. Isis will supply OncoGenex, and OncoGenex will purchase from Isis, the [***] grams of OGX-011 API in Isis' possession as of the Amendment Effective Date for a purchase price of [***] in accordance with the terms and conditions of Purchase Order No. 184, dated February 14, 2006, issued by OncoGenex to Isis (including without limitation the specifications, warranties and other obligations set forth in the Terms and Conditions of Purchase attached thereto, other than the purchase price and payment terms), with the same effect, and to the same extent, as if such supply and purchase had been made pursuant to such Purchase Order. In connection therewith, Isis shall deliver to OncoGenex an updated Certificate of Analysis dated not more than ninety (90) days prior to the date of delivery to OncoGenex. OncoGenex acknowledges and agrees that in order to perform the testing necessary to provide the updated certificate of analyses, Isis will need to use approximately [***] grams of such API. Within ninety (90) days following the receipt by OncoGenex of such API and such Certificate of Analysis, each provided in accordance herewith, OncoGenex shall pay to Isis the purchase price set forth in this Section 4.3 and take delivery of the API purchased by OncoGenex hereunder plus approximately [***] grams of API previously purchased by OncoGenex.

Section 4.4 **Diligence.** OncoGenex will use Commercially Reasonable Efforts to develop and commercialize OGX-011 and Products.

ARTICLE 5
DEVELOPMENT & COMMERCIALIZATION

Section 5.1 **Development, Commercialization and Regulatory Responsibilities.** OncoGenex will have sole responsibility, including without limitation sole responsibility for all funding, resourcing and decision making, for all further development and commercialization with respect to OGX-011 and Products. OncoGenex hereby assumes all regulatory responsibilities in connection with OGX-011 and Products, including sole responsibility for all Regulatory Documents and for obtaining all regulatory approvals. OncoGenex will comply with all Applicable Laws in connection with the development and commercialization of OGX-011 and Products. All INDs, NDAs, MAAs and other regulatory filings for OGX-011 and Products will be owned by OncoGenex.

Section 5.2 **Reports by OncoGenex.** At Isis' request, after the first anniversary of the Amendment Effective Date, OncoGenex will provide an annual report to Isis summarizing

OncoGenex' development and commercialization activities over the past year regarding the Product in substantially the form, and with substantially the content, of OncoGenex' regular reports provided to its board of directors regarding the Product. In addition, OncoGenex will promptly respond to any reasonable follow-up questions Isis may have regarding such reports solely to the extent necessary to determine whether OncoGenex is in compliance with its obligations to use Commercially Reasonable Efforts under Section 4.4. Isis shall have the right to use such reports solely to reasonably determine whether OncoGenex is in compliance with its obligations to use Commercially Reasonable Efforts under Section 4.4.

Section 5.3 **Safety Database.** Isis maintains a database that includes information regarding the safety and tolerability of its drug compounds, individually and as a class, including information discovered during pre-clinical and clinical development (the "Isis Database").

5.3.1 To the extent OncoGenex and its Affiliates have collected data and information specifically regarding Products, and subject to Applicable Law, including, without limitation, all applicable privacy laws, rules and regulations (such as the Health Insurance Portability Accountability Act), any applicable informed consents, and any obligations or restrictions imposed by Third Party clinical sites relating to dissemination or use of such data and information, in an effort to maximize understanding of the safety profile and pharmacokinetics of Isis compounds, OncoGenex will provide Isis with the following: (a) copies of [***] and [***] summary reports, and [***] final reports, in each case specifically regarding Products, and (b) in connection with any reported [***] (including any follow-up or amended reports) specifically regarding a Product, the following [***] regarding the applicable Product: (i) [***]; (ii) [***] usage; (iii) particulars of [***]; (iv) [***] history [***]; and (v) [***]. All such data and information disclosed by OncoGenex to Isis in connection with this Section 5.3, together with any data and information related to the [***] of each Product and any [***], will be OncoGenex' Confidential Information. Isis shall use such Confidential Information solely for the purpose of populating the Isis Database, and for no other purpose. Isis shall not disclose any such Confidential Information to any Third Party; *provided, however*, that Isis may conduct analyses to keep Isis and its partners informed regarding class generic safety and pharmacokinetic properties of ASOs so long as Isis does not disclose to such Third Parties the identity of the applicable Product, Clusterin as the target, OncoGenex or its Affiliates (or any information that would foreseeably reveal the identity of the applicable Product, Clusterin as the gene target, OncoGenex or its Affiliates) or any patient identifying information.

5.3.2 To the extent that [***] OncoGenex under this Agreement collects safety and tolerability data or information specifically regarding a Product, OncoGenex shall use commercially reasonable efforts to obtain from such sublicensee (a) the right to provide to Isis (whether through OncoGenex or its Affiliate, or directly from such sublicensee) the [***] described in [***] and (b) the right of Isis to [***] for the purposes described in [***]. Only sublicensees that agree to provide such [***] and grant Isis the right to use such [***] as set forth herein, will have the right to access the results of any queries requested by OncoGenex. If and when Isis identifies safety, pharmacokinetic or other related issues that may be relevant to a Product [***] Isis will promptly inform OncoGenex of such issues, and if requested, provide the data and information supporting Isis' conclusions regarding such issues. In addition, at OncoGenex' reasonable request and at no cost to OncoGenex, Isis will [***] the Isis Database to provide OncoGenex information regarding [***] or other related issues.

5.3.3 To the extent OncoGenex or its Affiliate obtains safety and tolerability data or information specifically regarding a Product, and such data or information is subject to any restrictions or obligations imposed by a Third Party clinical site, OncoGenex shall use commercially reasonable efforts to obtain from such Third Party clinical site (a) the right to provide to Isis the data and information described in this Section 5.3, and (b) the right of Isis to use such data and information for the purposes described in this Section 5.3.

ARTICLE 6
FINANCIAL PROVISIONS

Section 6.1 **Initial Payment by OncoGenex.** The Parties acknowledge and agree that OncoGenex paid to Isis $500,000 (U.S.) under section 5.1 of the Original Collaboration Agreement.

Section 6.2 **Royalty Payments by OncoGenex; Royalty Term.**

6.2.1 **Royalty Rate.** In consideration of Isis' collaborative efforts under the Original Collaboration Agreement and the licenses and assignments granted hereunder, OncoGenex will pay Isis a base royalty of [***]% of the Net Sales of a Product. In addition, OncoGenex will pay Isis [***]% of Royalty Revenue in excess of [***]% of Net Sales of Third Parties to a maximum additional royalty payable to Isis of [***]% of Net Sales of Third Parties.

6.2.2 [***]**.** Notwithstanding anything to the contrary in this Agreement, if (i) OncoGenex has an agreement with a Third Party for the further development or commercialization of a Product pursuant to which such Third Party is selling the Product (a "Commercialization Agreement"), (ii) under such Commercialization Agreement the [***] by such Third Party to OncoGenex [***] of such Product under such Commercialization Agreement [***] and (iii) a [***] in any country would not be infringed by the making, using or selling of a Product in such country by an unauthorized party, then with respect to such Product in such country, (a) the applicable [***]% base royalty rate, and the [***]% threshold for and [***]% cap on the additional royalty, under Section 6.2.1 above shall be [***] as such [***] and (b) the aggregate royalty owing to Isis shall not exceed [***] of the Royalty Revenue retained by OncoGenex.

6.2.3 [***]**.**

(a) Notwithstanding anything to the contrary in this Agreement, subject to Section 6.2.3(c), if (i) OncoGenex has a Commercialization Agreement, and (ii) under such Commercialization Agreement the [***] to OncoGenex on the [***] under such agreement because [***] then with respect to such Product, the applicable [***]% royalty rate, and the [***]% threshold and the [***] on the additional royalty under Section 6.2.1 above shall be reduced in the same manner and in the same proportion as such [***].

(b) Notwithstanding anything to the contrary in this Agreement, subject to Section 6.2.3(c) if (i) OncoGenex does not have a Commercialization Agreement, and (ii) in any quarter, there are one or more [***] OncoGenex may [***] above on a country-by-country and Product-by-Product basis by [***] represents of the [***] in such country as reported by IMS plus (b) [***] in such country, in each case in such quarter. By way of example, if in any quarter

the [***] in a country represents 50% of the [***] of the Product plus all [***] OncoGenex may reduce the royalties due to Isis under Section 6.2.1 by [***] in such country. Nothing in this Section 6.2.3 shall modify the obligations of OncoGenex under [***] required pursuant to the [***] Agreement and the [***] Agreement.

(c) This Section will not apply to [***] by Isis or a Third Party in a country under a license granted by Isis pursuant to Section 12.2.2, unless a Valid Claim within the Product-Specific Technology Patents, Isis Core Technology Patents, Isis Manufacturing Patents or Joint Patents in such country would not be infringed by the making, using or selling of such Product in such country by an unauthorized party.

6.2.4 Third Party Payments. In addition to the royalty set forth in Section 6.2.1, OncoGenex will pay to Isis (i) a royalty of [***]% of Net Sales of such Product to the extent required pursuant to the [***] Agreement; and (ii) a royalty of [***]% of Net Sales of such Product to the extent required pursuant to the [***] Agreement. In the event that Isis negotiates a reduction or elimination of the royalties with [***] or [***] following the Amendment Effective Date, the royalties due under the referenced license agreements will still be paid to Isis.

6.2.5 Noncumulative Relief. If the conditions described in Sections 6.2.2 and 6.2.3 have been met such that, under both provisions, OncoGenex would be entitled to [***] OncoGenex may [***] by applying the greater of the [***] such that under no circumstances will Sections 6.2.2 and 6.2.3 work together to cumulatively [***].

Section 6.3 **Royalty Term.** Royalties payable under Section 6.2 will be payable for each Product on a country-by-country basis from the first commercial sale of a Product in such country until the date that is the later of (i) [***] after the first commercial sale of a Product in such country or (ii) the expiration of the last to expire Valid Claim within the Product-Specific Technology Patents, Isis Core Technology Patents, Isis Manufacturing Technology or Joint Patents which would be infringed by the making, using or selling of the applicable Product in the applicable country by an unauthorized party.

Section 6.4 **Timing of Royalty Payments; Preliminary Report.**

6.4.1 The royalties calculated in Sections 6.2 or 6.3 will become due and payable within 40 days after each respective Royalty Due Date and will be calculated in respect of the Net Sales in the calendar quarter period ending with the applicable Royalty Due Date; *provided, however*, that if the royalties are adjusted in accordance with Section 6.2.3, then such royalties will become due and payable within the later of (a) forty (40) days after each respective Royalty Due Date, and (b) fifteen (15) days after the applicable IMS data is available for the applicable quarter as necessary to fully calculate the royalty reduction under Section 6.2.3. Furthermore, OncoGenex agrees to supply Isis the information Isis reasonably requires to comply with any third party payments under Section 6.3. In the event the applicable IMS data is no longer available, the Parties agree to negotiate in good faith a reasonable, mutually-acceptable data source to be used in place of IMS data for purposes of calculating the royalty reduction under Section 6.2.3. In the event the applicable IMS data (or other reasonable, mutually-acceptable data described above) is only available on a date that is significantly later than forty (40) days after the respective Royalty Due Date, the Parties agree to negotiate in good faith a reasonable,

mutually-acceptable mechanism providing for the payment by OncoGenex, within forty (40) days after the respective Royalty Due Date, of the estimated royalty payment for a quarter based on commercially reasonable assumptions, and the prompt true-up (in the form of an additional payment, repayment or credit, as applicable) of such estimated payment once the actual royalty payment for such quarter may be calculated.

6.4.2 In addition, during the Term following the first commercial sale of any Product, within 10 Business Days after the Royalty Due Date, OncoGenex will provide Isis a preliminary non-binding quarterly royalty report estimating the total Net Sales of Product and royalty payable for such calendar quarter. Unless required by applicable law or OncoGenex has already publicly disclosed such information, Isis shall not directly or indirectly in any manner whatsoever, publicly disclose the information contained in the preliminary royalty report estimate without first confirming such information against the payment made by OncoGenex under Section 6.4.1 above for the applicable period, and without expressly acknowledging that such information is a preliminary non-binding estimate only. Notwithstanding anything to the contrary in this Agreement, (a) any breach by Isis of its obligations under Section 6.4.2 shall constitute a material breach under this Agreement, and (b) OncoGenex will not be liable to Isis for any Loss Isis may suffer as a result of Isis publicly disclosing information contained in such a preliminary non-binding quarterly royalty report estimate.

Section 6.5 **Non-Royalty Revenue Payments by OncoGenex.** Non-Royalty Revenue will be allocated between the Parties based on the timing of when OncoGenex signs a sublicensing agreement with a Third Party for the Product as follows:

Timing of signing a sublicensing agreement	Isis share of Non-Royalty Revenue	OncoGenex share of Non-Royalty Revenue
(a) Prior to the initiation (i.e. first patient dosed) of a first Registration Clinical Trial for a Product	[***]%	[***]%
(b) After (a) but prior to enrolling 20% of the planned patients in the first Registration Clinical Trial for a Product	[***]%	[***]%

(c) After (b) but prior to obtaining marketing approval from a Regulatory Authority	[***]%	[***]%
(d) After (c)	[***]%	[***]%

6.5.1 Third Party Payments on Non-Royalty Revenue. Isis will be solely responsible for passing through the Third Party Payments owing to [***] and [***] on Non-Royalty Revenue, if any.

Section 6.6 **Timing of Non-Royalty Revenue Payments.** Isis share of Non-Royalty Revenue calculated in Section 6.5 will become due and payable within twenty-one (21) days after receipt of the applicable Non-Royalty Revenue by OncoGenex.

Section 6.7 **Payment Method.** Any amounts due to Isis pursuant to this Agreement will be paid in U.S. dollars by wire transfer in immediately available funds to an account designated by Isis. Any payments or portions thereof due hereunder which are not paid on the date such payments are due under this Agreement will bear interest at a rate equal to the lesser of the prime rate as published in *The Wall Street Journal*, Eastern Edition, on the first day of each calendar quarter in which such payments are overdue, plus two percent (2%), or the maximum rate permitted by law, whichever is lower, calculated on the number of days such payment is delinquent, compounded monthly.

Section 6.8 **Currency; Foreign Payments.** If any currency conversion will be required in connection with any payment hereunder, such conversion will be made by using the daily noon buying rates as published by the Federal Reserve Bank of New York on the last business day of the calendar quarter to which such payments relate. If at any time legal restrictions prevent the prompt remittance of any payments in any jurisdiction, OncoGenex may notify Isis and make such payments by depositing the amount thereof in local currency in a bank account or other

depository in such country in the name of Isis or its designee, and OncoGenex will have no further obligations under this Agreement with respect thereto.

Section 6.9 **Taxes.** OncoGenex may deduct from any amounts it is required to pay to Isis pursuant to this Agreement an amount equal to that withheld for or due on account of any taxes (other than taxes imposed on or measured by net income) or similar governmental charge imposed on Isis by a jurisdiction of OncoGenex ("Withholding Taxes"). OncoGenex will provide Isis a certificate evidencing payment of any Withholding Taxes hereunder within 30 days of such payment. OncoGenex will notify Isis as soon as practicable once OncoGenex has determined it will deduct the amount of any Withholding Taxes from its payments to Isis under this Section 6.9. Each Party agrees to cooperate with the other Party in claiming refunds or exemptions from such deductions or withholdings under any relevant agreement or treaty which is in effect. The Parties shall discuss applicable mechanisms for minimizing such taxes to extent possible in compliance with Applicable Law. In addition, the Parties shall cooperate in accordance with Applicable Law to minimize indirect taxes (such as value added tax, sales tax, consumption tax and other similar taxes) in connection with this Agreement.

Section 6.10 **Records Retention; Audit.**

6.10.1 Regulatory Records. With respect to the subject matter of this Agreement, OncoGenex will maintain, or cause to be maintained, records of its research, development, manufacturing and commercialization activities, including all Regulatory Documentation, pursuant to its standard operating procedures. All Regulatory Documentation will be retained for a period at least as may be required by Applicable Law.

6.10.2 Record Retention. OncoGenex will maintain (and will ensure that its sublicensees will maintain) complete and accurate books, records and accounts that fairly reflect Revenue and the royalties payable to Isis under this Agreement (including the calculation of Net Sales and any adjustments under Section 6.2) with respect to the Product in sufficient detail to confirm the accuracy of any payments required hereunder and in accordance with GAAP, which books, records and accounts will be retained until the later of (i) 3 years after the end of the period to which such books, records and accounts pertain, and (ii) the expiration of the applicable tax statute of limitations (or any extensions thereof), or for such longer period as may be required by Applicable Law.

6.10.3 Audit. Isis will have the right to have an independent certified public accounting firm of nationally recognized standing, reasonably acceptable to OncoGenex, have access during normal business hours, and upon reasonable prior written notice, to such of the records of OncoGenex as may be reasonably necessary to verify the accuracy of Revenues for any calendar quarter or calendar year ending not more than 24 months prior to the date of such request; *provided, however*, that Isis will not have the right to conduct more than one such audit in any Calendar Year except as provided below. Isis will bear the cost of such audit unless the audit reveals a variance of more than 5% from the reported results, in which case OncoGenex will bear the cost of the audit. Isis will have the right to audit previous years, if such years have not been previously audited, if the audit reveals a variance of more than 5% from the reported results. Isis will bear the cost of such previous year audits unless such audits reveal a variance of more than

5%. The results of such accounting firm will be final and binding upon each of Isis and OncoGenex, absent manifest error.

6.10.4 Payment of Additional Amounts. If, based on the results of such audit, additional payments are owed by OncoGenex under this Agreement, OncoGenex will make such additional payments, with interest from the date originally due at the rate of 1% per month, within 60 days after the date on which such accounting firm's written report is delivered to OncoGenex.

6.10.5 Confidentiality. Isis will treat all information subject to review under this Section 6.10 as OncoGenex' Confidential Information in accordance with the confidentiality provisions of Article 7 and will cause its accounting firm to enter into a reasonably acceptable confidentiality agreement with OncoGenex obligating such firm to maintain all such financial information in confidence pursuant to such confidentiality agreement. The accounting firm will disclose to Isis only whether the reports are correct or not and the amount of any discrepancy. No other information will be shared.

ARTICLE 7
CONFIDENTIALITY

Section 7.1 **Disclosure and Use Restriction.** Except as expressly provided herein, the Parties agree that, for the Term and for five (5) years thereafter, each Party will keep completely confidential and will not publish, submit for publication or otherwise disclose, and will not use for any purpose except for the purposes contemplated by this Agreement, any Confidential Information received from the other Party.

7.1.1 Authorized Disclosure. Each Party may disclose Confidential Information of the other Party to the extent that such disclosure is:

(a) made in response to a valid order of a court of competent jurisdiction; *provided, however*, that such Party will first have given notice to such other Party and given such other Party a reasonable opportunity to quash such order and to obtain a protective order requiring that the Confidential Information and documents that are the subject of such order be held in confidence by such court or agency or, if disclosed, be used only for the purposes for which the order was issued; and provided further that if a disclosure order is not quashed or a protective order is not obtained, the Confidential Information disclosed in response to such court or governmental order will be limited to that information which is legally required to be disclosed in response to such court or governmental order;

(b) otherwise required by law; *provided, however*, that the disclosing Party will provide such other Party with notice of such disclosure in advance thereof to the extent practicable;

(c) made by such Party to the Regulatory Authorities as required in connection with any filing, application or request for Regulatory Approval; *provided, however*, that reasonable measures will be taken to assure confidential treatment of such information;

(d) made by such Party, in connection with the performance of this Agreement, to permitted sublicensees, licensors, directors, officers, employees, consultants, representatives or agents, each of whom prior to disclosure must be bound by obligations of confidentiality and non-use at least equivalent in scope to those set forth in this Article 7; or

(e) made by such Party to existing or potential acquirers; existing or potential pharmaceutical collaborators (to the extent contemplated hereunder); investment bankers; existing or potential investors, merger candidates, partners, venture capital firms or other financial institutions or investors for purposes of obtaining financing; or, bona fide strategic potential partners; each of whom prior to disclosure must be bound by obligations of confidentiality and non-use at least equivalent in scope to those set forth in this Article 7.

Section 7.2 **Publicity.**

7.2.1 Press Releases Regarding Agreement. Upon execution of this Agreement, the Parties shall issue a joint press release announcing the existence of this Agreement in a form and substance agreed to in writing by the Parties. Each Party agrees not to issue any other press release or other public statement disclosing other information relating to this Agreement or the transactions contemplated hereby without the prior written consent of the other Party, except for those communications required by Applicable Law or court order, disclosures of information for which consent has previously been obtained, and information of a similar nature to that which has been previously disclosed publicly with respect to this Agreement, each of which will not require advance approval, but will be provided to the other Party as soon as practicable after the release or communication thereof.

7.2.2 Press Releases Regarding Products.

(a) OncoGenex may publish, present or otherwise disclose results regarding OGX-011 or Product to the public at its sole discretion; *however*, any press release or other similar public communication by either Party related to a Product's efficacy or safety data and/or results, will be submitted to the other Party for review at least 4 Business Days in advance of such proposed public disclosure. Notwithstanding the foregoing, if the Party is making a disclosure that is reasonably required by applicable law, regulation or court order and cannot practically submit the disclosure to the other Party within the 4 Business Day advance notice period above, the disclosing Party may provide the other Party the disclosure [***] advance notice as is practical under the circumstances, but in any event at least [***] written notice. OncoGenex may satisfy its notice obligation under this Section 7.2.2(a) by emailing and telephoning either Isis' Chief Executive Officer or Chief Operating Officer, and Isis may satisfy its notice obligation under this Section Section 7.2.2(a) by emailing and telephoning OncoGenex' Chief Executive Officer.

(b) In addition, each Party will immediately notify (and provide as much advance notice as possible to) the other of any event materially related to Product (including any regulatory approval) so that the Parties may analyze the need to or desirability of publicly disclosing or reporting such event.

ARTICLE 8
TECHNOLOGY AND PATENTS

Section 8.1 **Ownership.**

8.1.1 Ownership of Technology and Patents.

(a) As between OncoGenex and Isis, Isis will solely own all right, title and interest to the Isis Core Technology, Isis Core Technology Patents, Isis Manufacturing Technology and Isis Manufacturing Patents.

(b) As between OncoGenex and Isis, OncoGenex will solely own all right, title and interest to the OncoGenex Technology and OncoGenex Technology Patents.

(c) Except as otherwise set forth in clauses (a) and (b) above, and in Section 4.2.1, as between OncoGenex and Isis, (i) OncoGenex will solely own all right, title and interest in all discovery, invention, data, information, trade secret, know-how or other technology (the "Technology") conceived or reduced to practice solely by employees or agents of OncoGenex, together with all patents and other intellectual property rights therein and

thereto; (ii) Isis will solely own all right, title and interest in and to all Technology conceived or reduced to practice solely by employees or agents of Isis, together with all patents and other intellectual property rights therein and thereto; and (iii) OncoGenex and Isis will jointly own all right, title and interest in all Joint Technology, together with all patents and other intellectual property rights therein and thereto. Each party will have the right, subject to the provisions of this Agreement, to freely exploit, transfer, license or encumber its rights in any Joint Patents without the consent of, or payment or accounting to, the other party.

8.1.2 Ownership of Regulatory Documentation. All Regulatory Documentation with respect to the Product will be owned by OncoGenex.

Section 8.2 **Prosecution of Patents.**

8.2.1 Isis Rights. Isis will have the sole right, at its cost and expense and at its sole discretion, to obtain, prosecute and maintain throughout the world the Isis Patent Rights, including, but not limited to the Isis Core Technology Patents and the Isis Manufacturing Patents, but excluding the Product-Specific Technology Patents and the Joint Patents. Isis will keep OncoGenex informed of the status of all Isis Core Technology Patents and Isis Manufacturing Patents by way of an annual listing and reasonably detailed written status report.

8.2.2 OncoGenex Rights. OncoGenex will have the sole right, at its cost and expense and at its sole discretion, to file, obtain, prosecute and maintain throughout the world any OncoGenex Technology Patents, Product-Specific Technology Patents and the Joint Patents.

8.2.3 Cooperation. Each Party will cooperate in the preparation, filing, prosecution, and maintenance of the other Party's Patents, the Product-Specific Technology Patents and the Joint Patents, as required. Such cooperation includes promptly executing all papers and instruments and requiring employees to execute such papers and instruments as reasonable and

appropriate so as to enable such other Party, to file, prosecute, and maintain its Patents in any country.

Section 8.3 **Enforcement of Patents.**

8.3.1 Rights and Procedures. If Isis or OncoGenex determines that any Isis Patent Rights or OncoGenex Patent Rights are being infringed by a Third Party's activities and that such infringement could affect the exercise by OncoGenex of its rights under this Agreement, it will promptly notify the other Party in writing and provide such other Party with any evidence of such infringement that is reasonably available.

(a) Isis Core Technology Patents and Isis Manufacturing Patents. Subject to 8.3.1(e) Isis will have the sole right, but not the obligation, at its own expense, to remove infringement of Isis Core Technology Patents and Isis Manufacturing Patents using commercially appropriate steps, including the filing of an infringement suit or taking other similar action, and OncoGenex or a Third Party licensee of the Product will have the right, at its own expense, to be represented in any such action; *provided*, *however*, that (i) if Isis fails to bring an action or proceeding within ninety (90) days following notice of such infringement, or earlier notifies OncoGenex or a Third Party licensee of the Product in writing of its intent not to take such steps, and (ii) the infringement is likely to have a material adverse effect on OncoGenex' or a sub-licensee' development, manufacture, production, release or commercialization of the Product, then OncoGenex and/or the Third Party licensee of the Product will meet with Isis to determine whether to defend against such infringement, and if the Parties mutually agree in writing to proceed in defending such infringement, Isis will remove the infringement using commercially appropriate steps, and OncoGenex or the Third Party will share in the reasonable costs incurred relating to the removal of any such infringement on an equal basis. If however, (i) the Parties cannot mutually agree in writing to proceed in removing such infringement, (ii) the product in question is a Competing Product, and (iii) OncoGenex requests in writing that Isis remove such infringement (an "OncoGenex Mandate"), then Isis (at OncoGenex' sole expense) will remove the infringement using commercially appropriate steps. In either case, Isis may not settle, or otherwise consent to an adverse judgment in, such infringement that diminishes the rights or interests of OncoGenex without the prior express written consent of OncoGenex.

(b) In the event of an (i) OncoGenex Mandate (ii) Isis refuses to remove the infringement in a country using commercially appropriate steps (as determined, if necessary, in accordance with the dispute resolution provisions in Section 13.15) and (iii) such Competing Product is actually being sold in such country, then the [***].

(c) OncoGenex Technology Patents. Subject to 8.3.1(e) OncoGenex will have the sole right, but not the obligation, at its own expense, to remove infringement of OncoGenex Technology Patents using commercially appropriate steps, including the filing of an infringement suit or taking other similar action, and Isis will have the right, at its own expense, to be represented in any such action.

(d) Product-Specific Technology Patents and Joint Patents. Subject to 8.3.1(e) OncoGenex will have the sole right, but not the obligation, at its own expense, to

remove infringement of Product-Specific Technology Patents and Joint Patents using commercially appropriate steps, including the filing of an infringement suit or taking other similar action, and Isis will have the right, at its own expense, to be represented in any such action; *provided*, *however*, that if the Product has not been sublicensed to a Third Party and OncoGenex fails to bring an action or proceeding within ninety (90) days following notice of such infringement, or earlier notifies Isis in writing of its intent not to take such steps, Isis will have the right to do so at its expense, and OncoGenex will have the right, at its own expense, to be represented in any such action. Notwithstanding the foregoing, if the infringement is likely to have a material adverse effect on Isis' economic interest in the Product's development or commercialization, Isis and OncoGenex will meet to determine whether to defend against such infringement, and if the Parties mutually agree to proceed in defending such infringement, OncoGenex will remove the infringement using commercially appropriate steps, and Isis and OncoGenex will share in the reasonable costs incurred relating to the removal of any such infringement on an equal basis.

(e) Cooperation. The Party not enforcing the applicable Patent will provide reasonable assistance to the other Party, including, but not limited to, providing access to relevant documents and other evidence, making its employees available at reasonable business hours, and joining the action to the extent necessary to allow the enforcing Party to maintain the action.

8.3.2 Recovery. Any amounts recovered by either or both Parties, including Third Party licensees in connection with or as a result of any action contemplated by Section 8.3.1, whether by settlement or judgment, will be used to reimburse the Parties, including Third Party licensees for their reasonable costs and expenses in making such recovery (which amounts will be allocated pro rata if insufficient to cover the totality of such expenses). Furthermore, if Isis is enforcing Party under Section 8.3.1(a) or OncoGenex is the enforcing party, after reimbursing the Parties in accordance with the preceding sentence, OncoGenex will retain any remainder of the recovery as Net Sales and royalties will be payable by OncoGenex to Isis with respect to such Net Sales in accordance with this Agreement. If Isis is the enforcing party other than as set forth in Section 8.3.1(a), after reimbursing the Parties in accordance with the first sentence of this Section, any remainder will be kept by Isis.

Section 8.4 **Third Party Litigation.** In the event that a Third Party institutes a patent infringement suit (including any suit alleging the invalidity or unenforceability of the Patents of a Party) against either Party or Third Party licensees during the Term of this Agreement, alleging that any of the activities hereunder infringes one or more patent or other intellectual property rights held by such Third Party (an "Infringement Suit"), the Parties will cooperate with one another in defending such suit. Isis will have the sole right to control any defense of any such claim involving alleged infringement of Third Party rights by Isis' activities at its own expense and by counsel of its own choice, and OncoGenex will have the right, at its own expense, to be represented in any such action by counsel of its own choice. OncoGenex will have the sole right to control any defense of any such claim involving alleged infringement of Third Party rights by OncoGenex' activities, or that relates to the development, manufacture, production, release and commercialization of the Product, at its own expense and by counsel of its own choice, and Isis will have the right, at its own expense, to be represented in any such action by additional counsel of its own choice at its own expense.

Section 8.5 **No Challenge.** During the term of this Agreement, OncoGenex, its Affiliates and sublicensees will not, directly or indirectly, and will not collaborate with, or otherwise authorize any Third Party to challenge any Isis Patent Rights licensed by Isis to OncoGenex under this Agreement, including through opposition, re-examination, nullity or revocation proceeding, or other available administrative mechanism; provided, however, that, notwithstanding the foregoing, OncoGenex, its Affiliates and sublicensees shall have the right to comply with a subpoena duly issued in good faith by a Third Party, court or administrative order, or similar legal process for testimony or the production of documents.

ARTICLE 9
TERM AND TERMINATION

Section 9.1 **Term.** The term of this Agreement (the "Term") will continue in effect until such time as any Product is no longer being developed, manufactured, produced, released or commercialized hereunder, or unless terminated at an earlier date in accordance with the terms and conditions set forth in this Article 9. Isis will have the right to terminate this Agreement and/or any license granted by it hereunder solely in accordance with Article 12.

Section 9.2 **Rights in Bankruptcy.** All rights and licenses granted under or pursuant to this Agreement by Isis to OncoGenex are, and will otherwise be deemed to be, for purposes of Section 365(n) of the United States Bankruptcy Code, licenses of rights to "intellectual property" as defined under Section 101 of the United States Bankruptcy Code. The Parties agree that OncoGenex, as a licensee of such rights under this Agreement, will retain and may fully exercise all of its rights and elections under the United States Bankruptcy Code. The Parties further agree that, in the event of the commencement of a bankruptcy proceeding by or against Isis under the United States Bankruptcy Code, OncoGenex will be entitled to a complete duplicate of (or complete access to, as appropriate) any such intellectual property and all embodiments of such intellectual property, which, if not already in OncoGenex' possession, will be promptly delivered to it (a) upon any such commencement of a bankruptcy proceeding upon OncoGenex' written request therefor, unless Isis elects to continue to perform all of its obligations under this Agreement or (b) if not delivered under clause (a) above, following the rejection of this Agreement by or on behalf of Isis upon written request therefor by OncoGenex.

Section 9.3 **Consequences of Expiration or Termination.**

9.3.1 Licenses. Upon expiration of the Term of this Agreement in accordance with Section Section 9.1 and payment of all amounts owed pursuant to this Agreement, the licenses granted by Isis to OncoGenex hereunder will terminate.

9.3.2 Return of Information and Materials. Upon expiration of this Agreement pursuant to Section Section 9.1 or upon termination of this Agreement in its entirety by either Party pursuant to this Article 9, each Party, at the request of the other Party, will return all data, files, records and other materials in its possession or control relating to such other Party's Technology, or containing or comprising such other Party's Information and Inventions or other Confidential Information and, in each case, to which the returning Party does not retain rights hereunder (except one copy of which may be retained for archival purposes). Notwithstanding

the foregoing, each Party may retain one (1) copy of the other Party's Confidential Information for its legal archives.

Section 9.4 **Accrued Rights; Surviving Obligations.**

9.4.1 Accrued Rights. Termination or expiration 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.

9.4.2 Survival. Articles 7, 10, 12 and 13 of this Agreement, and Sections 4.2.1, 6.10, 8.1, 9.3, 9.4 and 11.4 will survive expiration or termination of this Agreement for any reason.

ARTICLE 10
INDEMNIFICATION AND INSURANCE

Section 10.1 **Indemnification of Isis.** OncoGenex will indemnify Isis, and their respective directors, officers, employees and agents, and defend and hold each of them harmless, from and against any and all losses, damages, liabilities, costs and expenses (including reasonable attorneys' fees and expenses)

but only to the extent arising from or occurring as a result of any and all liability suits, investigations, claims, demands or actions by a Third Party (collectively, "Losses" and each a "Loss") to the extent arising from or occurring as a result of (a) whether or not negligence is found, the development, manufacture, use, handling, storage, sale or other commercialization or disposition of OGX-011 or any Product by OncoGenex or its Affiliates or licensees, (b) any material breach by OncoGenex of this Agreement, or (c) the gross negligence or willful misconduct on the part of OncoGenex or its licensees or sublicensees in performing any activity contemplated by this Agreement, except for those Losses for which Isis has an obligation to indemnify OncoGenex pursuant to Section 10.2, as to which Losses each Party will indemnify the other to the extent of their respective liability for the Losses.

Section 10.2 **Indemnification of OncoGenex.** Isis will indemnify OncoGenex, and their respective directors, officers, employees and agents, and defend and save each of them harmless, from and against any and all Losses to the extent arising from or occurring as a result of (a) any material breach by Isis of this Agreement, or (b) the gross negligence or willful misconduct on the part of Isis or its licensees or sublicensees in performing any activity contemplated by this Agreement, except for those Losses for which OncoGenex has an obligation to indemnify Isis pursuant to Section 9.1, as to which Losses each Party will indemnify the other to the extent of their respective liability for the Losses.

Section 10.3 **Indemnification Procedure.**

10.3.1 Notice of Claim. The indemnified Party will give the indemnifying Party prompt written notice (an "Indemnification Claim Notice") of any Loss upon which such indemnified Party intends to base a request for indemnification under Section 10.1 or Section 10.2, but in no event will the indemnifying Party be liable for any Losses that result from any delay in providing such notice. Each Indemnification Claim Notice must contain a description of the Loss and the nature and amount of such Loss (to the extent that the nature and amount of such Loss are known

at such time). The indemnified Party will furnish promptly to the indemnifying Party copies of all papers and official documents received in respect of such Loss. All indemnification claims in respect of a Party, its Affiliates or their respective directors, officers, employees and agents (collectively, the "Indemnitees" and each an "Indemnitee") will be made solely by such Party to this Agreement (the "Indemnified Party").

10.3.2 Third Party Claims. The obligations of an indemnifying Party under this Article 10 with respect to Losses arising from claims of any Third Party that are subject to indemnification as provided for in Section 10.1 or 10.2 (a "Third Party Claim") will be governed by and be contingent upon the following additional terms and conditions:

(a) Control of Defense. At its option, the indemnifying Party may assume the defense of any Third Party Claim by giving written notice to the Indemnified Party within 30 days after the indemnifying Party's receipt of an Indemnification Claim Notice. The assumption of the defense of a Third Party Claim by the indemnifying Party will not be construed as an acknowledgment that the indemnifying Party is liable to indemnify any Indemnitee in respect of the Third Party Claim, nor will it constitute a waiver by the indemnifying Party of any defenses it may assert against any Indemnitee's claim for indemnification. Upon assuming the defense of a Third Party Claim, the indemnifying Party may appoint as lead counsel in the defense of the Third Party Claim any legal counsel selected by the indemnifying Party. In the event the indemnifying Party assumes the defense of a Third Party Claim, the Indemnified Party will immediately deliver to the indemnifying Party all original notices and documents (including court papers) received by any Indemnitee in connection with the Third Party Claim. Should the indemnifying Party assume the defense of a Third Party Claim, the indemnifying Party will not be liable to the Indemnified Party or any other Indemnitee for any legal expenses subsequently incurred by such Indemnified Party or other Indemnitee in connection with the analysis, defense or settlement of the Third Party Claim. In the event that it is ultimately determined that the indemnifying Party is not obligated to indemnify, defend or hold harmless an Indemnitee from and against the Third Party Claim, the Indemnified Party will reimburse the indemnifying Party for any and all costs and expenses (including attorneys' fees and costs of suit) and any Losses incurred by the indemnifying Party in its defense of the Third Party Claim with respect to such Indemnitee.

(b) Right to Participate in Defense. Without limiting Section 10.3.2(a), any Indemnitee will be entitled to participate in, but not control, the defense of such Third Party Claim and to employ counsel of its choice for such purpose; *provided*, *however*, that such employment will be at the Indemnitee's own expense unless (i) the employment thereof has been specifically authorized by the indemnifying Party in writing, or (ii) the indemnifying Party has failed to assume the defense and employ counsel in accordance with Section 10.3.2(a) (in which case the Indemnified Party will control the defense).

(c) Settlement. With respect to any Losses relating solely to the payment of money damages in connection with a Third Party Claim and that will not result in the Indemnitee's becoming subject to injunctive or other relief or otherwise adversely affect the business of the Indemnitee in any manner, and as to which the indemnifying Party will have acknowledged in writing the obligation to indemnify the Indemnitee hereunder, the indemnifying Party will have the sole right to consent to the entry of any judgment, enter into any settlement or

otherwise dispose of such Loss, on such terms as the indemnifying Party, in its sole discretion, will deem appropriate. With respect to all other Losses in connection with Third Party Claims, where the indemnifying Party has assumed the defense of the Third Party Claim in accordance with Section 9.3.2(a), the indemnifying Party will have authority to consent to the entry of any judgment, enter into any settlement or otherwise dispose of such Loss provided it obtains the prior written consent of the Indemnified Party (which consent will not be unreasonably withheld or delayed). The indemnifying Party will not be liable for any settlement or other disposition of a Loss by an Indemnitee that is reached without the written consent of the indemnifying Party. Regardless of whether the indemnifying Party chooses to defend or prosecute any Third Party Claim, no Indemnitee will admit any liability with respect to, or settle, compromise or discharge, any Third Party Claim without the prior written consent of the indemnifying Party.

(d) Cooperation. Regardless of whether the indemnifying Party chooses to defend or prosecute any Third Party Claim, the Indemnified Party will, and will cause each other Indemnitee to, cooperate in the defense or prosecution thereof and will furnish such records, information and testimony, provide such witnesses and attend such conferences, discovery proceedings, hearings, trials and appeals as may be reasonably requested in connection therewith. Such cooperation will include access during normal business hours afforded to the indemnifying Party to, and reasonable retention by the Indemnified Party of, records and information that are reasonably relevant to such Third Party Claim, and making Indemnitees and other employees and agents available on a mutually convenient basis to provide additional information and explanation of any material provided hereunder, and the indemnifying Party will reimburse the Indemnified Party for all its reasonable out-of-pocket expenses in connection therewith.

(e) Expenses. Except as provided above, the reasonable and verifiable costs and expenses, including fees and disbursements of counsel, incurred by the Indemnified Party in connection with any claim will be reimbursed on a calendar quarter basis by the indemnifying Party, without prejudice to the indemnifying Party's right to contest the Indemnified Party's right to indemnification and subject to refund in the event the indemnifying Party is ultimately held not to be obligated to indemnify the Indemnified Party.

Section 10.4 **Insurance.** OncoGenex shall maintain product liability insurance with respect to the development, manufacture and sale of Products hereunder by OncoGenex in such amount as OncoGenex customarily maintains with respect to the development, manufacture and sale of its similar products, but at a minimum an amount that is customarily maintained by similar companies in the life sciences industry with respect to the development, manufacture and sale of similar products. OncoGenex shall maintain such insurance for so long as it continues to develop, manufacture or sell any Product, and thereafter for so long as OncoGenex customarily maintains insurance covering the development, manufacture or sale of its similar products. Upon Isis' request, OncoGenex will provide Isis with a certificate of insurance evidencing such insurance.

ARTICLE 11
REPRESENTATIONS AND WARRANTIES

Section 11.1 **Representations, Warranties and Covenants.** Each Party hereby represents, warrants and covenants to the other Party as of the Amendment Effective Date as follows:

11.1.1 Corporate Authority. Such Party (a) has the power and authority and the legal right to enter into this Agreement and perform its obligations hereunder, and (b) 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. 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.

11.1.2 Litigation. Such Party is not aware of any pending or threatened litigation (and has not received any communication) that alleges that such Party's activities related to this Agreement have violated, or that by conducting the activities as contemplated herein such Party would violate, any of the intellectual property rights of any other party.

11.1.3 Consents, Approvals, etc. All necessary consents, approvals and authorizations of all Regulatory Authorities and other parties required to be obtained by such Party in connection with the execution and delivery of this Agreement and the performance of its obligations hereunder have been obtained.

11.1.4 Conflicts. The execution and delivery of this Agreement and the performance of such Party's obligations hereunder (a) do not conflict with or violate any requirement of Applicable Law or any provision of the articles of incorporation, bylaws or any similar instrument of such Party, as applicable, in any material way, and (b) do not conflict with, violate, or breach or constitute a default or require any consent under, any contractual obligation or court or administrative order by which such Party is bound.

11.1.5 No Default. Such Party is not aware of any breach by it of any representation, warranty, or covenant in the Original Collaboration Agreement.

Section 11.2 **Additional Representations and Warranties of Isis.**

11.2.1 Isis represents and warrants to OncoGenex that Isis is a corporation duly organized, validly existing and in good standing under the laws of the State of Delaware, and has full corporate power and authority and the legal right to own and operate its property and assets and to carry on its business as it is now being conducted and as it is contemplated to be conducted by this Agreement.

11.2.2 Isis represents and warrants to OncoGenex that the rights granted by Isis to OncoGenex as set forth in Article 4 include all necessary rights of Isis' technology, whether or not patented or patentable, which are owned or Controlled by Isis on the Amendment Effective Date and which are necessary or reasonably required for OncoGenex to research develop, make,

have made, use, sell, offer for sale, have sold and import the Product. Further, Isis represents and warrants to OncoGenex that Isis has not knowingly [***] whether or not patented or patentable, to develop, make or use OGX-011 under the Original Collaboration Agreement, that Isis could not [***] of this Agreement or that (in the case of broadly commercially available reagents, equipment and software) is not otherwise available on commercially reasonable terms along with the purchase or lease of such reagents, equipment and software.

11.2.3 Isis represents and warrants to OncoGenex that (i) Section 9.6 of the [***] Agreement states that the sublicense granted by Isis to OncoGenex under the [***] Agreement will survive termination of the [***] Agreement, and (ii) Section 4.3(b) of the [***] Agreement provides that if the [***] Agreement is terminated for any reason, then [***] will promptly negotiate in good faith a direct license of the sublicensed rights, on terms substantially similar to those contained in this Agreement, with OncoGenex, unless the actions or omissions of OncoGenex were a cause for termination of the [***] Agreement.

Section 11.3 **Additional Representations and Warranties of OncoGenex.** OncoGenex represents and warrants to Isis that OncoGenex is a corporation duly organized, validly existing and in good standing under the laws of Canada, and has full corporate power and authority and the legal right to own and operate its property and assets and to carry on its business as it is now being conducted and as it is contemplated to be conducted by this Agreement.

Section 11.4 **DISCLAIMER OF WARRANTY.** EXCEPT FOR THE EXPRESS WARRANTIES SET FORTH IN SECTIONS 11.1, 11.2 AND 11.3, ONCOGENEX AND ISIS MAKE NO REPRESENTATIONS AND GRANT NO WARRANTIES, EXPRESS OR IMPLIED, EITHER IN FACT OR BY OPERATION OF LAW, BY STATUTE OR OTHERWISE, AND ONCOGENEX AND ISIS EACH SPECIFICALLY DISCLAIM ANY OTHER WARRANTIES, WHETHER WRITTEN OR ORAL, OR EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF QUALITY, MERCHANTABILITY OR FITNESS FOR A PARTICULAR USE OR PURPOSE OR ANY WARRANTY AS TO THE VALIDITY OF ANY PATENTS OR THE NON-INFRINGEMENT OF ANY INTELLECTUAL PROPERTY RIGHTS OF THIRD PARTIES.

ARTICLE 12
BREACH

Section 12.1 **Material Breach by Isis.** Failure by Isis to comply with any of its material obligations contained herein (including, without limitation, its technology transfer obligations under Section 4.2) will entitle OncoGenex to give Isis notice specifying the nature of the material breach, requiring Isis to make good or otherwise cure such default, and stating its intention to trigger the provisions of this Article 12 if such default is not cured. If such default is not cured within ninety (90) days after the receipt of such notice (or, if such default cannot be cured within such ninety (90) day period, if Isis does not commence actions to cure such default within such period and thereafter diligently continue such actions or if such default is not otherwise cured within ninety (90) days after the receipt of such notice), then OncoGenex will be entitled to appeal to the Courts to enforce specific performance upon Isis without prejudice to any of its other rights conferred on it by this Agreement, and in addition to any other remedies available to

the Courts as remedy for the breach and to continue to develop or commercialize the Product independently of Isis in accordance with this Agreement.

Section 12.2 **Breach by OncoGenex.**

12.2.1 Failure to Pay. If OncoGenex is in material breach of OncoGenex' obligation to make a payment to Isis under Article 6, then Isis may deliver written notice of such breach to OncoGenex. OncoGenex will have thirty (30) days following such notice to cure such breach. If OncoGenex receives written notice of such breach and fails to cure such breach within the 30 day period, Isis may declare a breach hereunder upon thirty (30) days advance written notice to OncoGenex and such notice will effectively terminate this Agreement upon expiration of such thirty (30) day period.

12.2.2 Discontinued Development. In the event of a Discontinuance or if OncoGenex materially breaches its diligence obligations under Section 4.4 which material breach is not cured by OncoGenex within ninety (90) days after receipt of written notice from Isis describing such material breach in reasonably specific detail, then in any such case, as Isis' sole and exclusive remedy therefor, Isis will have the right to terminate the [***] under [***] upon thirty (30) days prior written notice to OncoGenex and in such case OncoGenex will grant to Isis a worldwide license or sublicense, as the case may be, to the OncoGenex Product-Specific Technology, OncoGenex Patents, OncoGenex Technology and any Product-Specific Technology Patents assigned to OncoGenex under Section 4.2.1 (in the case of OncoGenex Patents and OncoGenex Technology that are the subject of one or more Third Party agreements, such license or sublicense shall be subject to all restrictions and obligations (including financial obligations) under such Third Party agreements) existing as of such date solely to develop, make, have made, use, sell, offer for sale, have sold and import Nonexclusive Clusterin ASOs (and any products containing such Nonexclusive Clusterin ASOs). For purposes of this Section 12.2.2, "Nonexclusive Clusterin ASOs" means ASOs that act predominantly by [***] Clusterin [***] or that are [***] to Clusterin [***] *provided, however* that Nonexclusive Clusterin ASOs will not include any ASO that (a) acts to modulate [***] Clusterin and (b) either (i) has the same [***] as OGX-011 or (ii) at the time of such Discontinuance or breach OncoGenex, its Affiliates or sublicensees had [***] (each, an "Exclusive ASO"). Within ninety (90) days following the effectiveness of any termination by Isis, pursuant to this Section 12.2.2, of the [***] OncoGenex shall provide Isis with a list describing the [***].

ARTICLE 13
MISCELLANEOUS

Section 13.1 **Force Majeure.** Except for any failure to make any payment required under Article 6, neither Party will be held liable or responsible to the other Party or be deemed to have defaulted under or breached this Agreement for failure or delay in fulfilling or performing any term of this Agreement when such failure or delay is caused by or results from events beyond the reasonable control of the non-performing Party, including fires, floods, embargoes, shortages, epidemics, quarantines, war, acts of war (whether war be declared or not), insurrections, riots, civil commotion, strikes, lockouts or other labor disturbances, acts of God or acts, omissions or delays in acting by any governmental authority. The non-performing Party will notify the other Party of such force majeure within ten (10) days after such occurrence by giving written notice to

the other Party stating the nature of the event, its anticipated duration, and any action being taken to avoid or minimize its effect. The suspension of performance will be of no greater scope and no longer duration than is necessary and the non-performing Party will use Commercially Reasonable Efforts to remedy its inability to perform; *provided, however*, that in the event the suspension of performance continues for one-hundred and eighty (180) days after the date of the occurrence, the Parties will meet to discuss in good faith how to proceed in order to accomplish the development and commercialization of the Product as set forth in this Agreement.

Section 13.2 **Assignment.** Without the prior written consent of the other Party hereto, neither Party will sell, transfer, assign, delegate, pledge or otherwise dispose of, whether voluntarily, involuntarily, by operation of law or otherwise, this Agreement or any of its rights or duties hereunder; *provided, however*, that (i) either Party hereto may assign or transfer this Agreement or any of its rights or obligations hereunder without the consent of the other Party to any Third Party with which it has merged or consolidated, or to which it has transferred all or substantially all of its assets to which this Agreement relates if in any such event the Third Party assignee or surviving entity assumes in writing all of the assigning Party's obligations under this Agreement or (ii) Isis may assign or transfer its rights under Article 6 (but no liabilities) to a Third Party in connection with a royalty (or payment) factoring transaction. Any purported assignment or transfer in violation of this Section will be void *ab initio* and of no force or effect.

Section 13.3 **Severability.** If any provision of this Agreement is held to be illegal, invalid or unenforceable by a court of competent jurisdiction, such adjudication will not affect or impair, in whole or in part, the validity, enforceability, or legality of any remaining portions of this Agreement. All remaining portions will remain in full force and effect as if the original Agreement had been executed without the invalidated, unenforceable or illegal part.

Section 13.4 **Governing Law.** This Agreement will be governed by and construed in accordance with the laws of the Province of British Columbia without reference to any rules of conflicts of laws.

Section 13.5 **Notices.** All notices or other communications that are required or permitted hereunder will be in writing and delivered personally with acknowledgement of receipt, sent by facsimile (and promptly confirmed by personal delivery, registered or certified mail or overnight courier as provided herein), sent by nationally-recognized overnight courier or sent by registered or certified mail, postage prepaid, return receipt requested, addressed as follows: If to OncoGenex, to:

OncoGenex Technologies Inc.
#400 – 1001 West Broadway
Vancouver, BC V6H 4B1
Attention: President
Facsimile: (604) 736-3687

with a copy to:

Doug Seppala
DuMoulin Black LLP
10th Floor, 595 Howe Street
Vancouver, British Columbia V6C 2T5
Facsimile: (604) 687-3635

If to Isis, to:

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, California 92008-7208
Attention: Executive Vice President
Facsimile: (760) 268-4922

with a copy to:

Attention: General Counsel
Facsimile: (760) 603-2707

or to such other address as the Party to whom notice is to be given may have furnished to the other Party in writing in accordance herewith. Any such communication will be deemed to have been given (i) when delivered, if personally delivered or sent by facsimile on a Business Day, (ii) on the Business Day after dispatch, if sent by nationally-recognized overnight courier, and (iii) on the third business day following the date of mailing, if sent by mail. It is understood and agreed that this Section 13.6 is not intended to govern the day-to-day business communications necessary between the Parties in performing their duties, in due course, under the terms of this Agreement.

Section 13.6 **Entire Agreement; Modifications.** This Agreement sets forth and constitutes the entire agreement and understanding between the Parties with respect to the subject matter hereof and all prior agreements, understanding, promises and representations, whether written or oral, with respect thereto are superseded hereby, including without limitation the Original Collaboration Agreement. For clarity, the Parties acknowledge and agree that the Original Collaboration Agreement remains in effect in accordance with its terms with respect to the period between the Start Date and the Amendment Effective Date. Each Party confirms that it is not relying on any representations or warranties of the other Party except as specifically set forth herein. No amendment, modification, release or discharge will be binding upon the Parties unless in writing and duly executed by authorized representatives of both Parties.

Section 13.7 **Relationship of the Parties.** It is expressly agreed that the Parties will be independent contractors of one another and that the relationship between the Parties will not constitute a partnership, joint venture or agency. Neither Party will have the authority to make any statements, representations or commitments of any kind, or to take any action, which will be binding on the other, without the prior written consent of the other to do so. All persons employed by a Party will be employees of such Party and not of the other Party and all costs and

obligations incurred by reason of any such employment will be for the account and expense of such Party.

Section 13.8 **Cooperation.** Isis will provide reasonable assistance to OncoGenex in respect of partnering discussions, financing activities and regulatory filings to support the development and commercialization of the Product. Notwithstanding the foregoing, Isis will not be required to modify or waive any provision of this Agreement in connection with partnering discussions or financing activities to support the development and commercialization of the Product.

Section 13.9 **Waiver.** Any term or condition of this Agreement may be waived at any time by the Party that is entitled to the benefit thereof, but no such waiver will be effective unless set forth in a written instrument duly executed by or on behalf of the Party waiving such term or condition. The waiver by either Party hereto of any right hereunder or of the failure to perform or of a breach by the other Party will not be deemed a waiver of any other right hereunder or of any other breach or failure by said other Party whether of a similar nature or otherwise.

Section 13.10 **Counterparts.** This Agreement may be executed in two (2) or more counterparts, each of which will be deemed an original, but all of which together will constitute one and the same instrument.

Section 13.11 **No Benefit to Third Parties.** The representations, warranties, covenants and agreements set forth in this Agreement are for the sole benefit of the Parties hereto and their successors and permitted assigns, and they will not be construed as conferring any rights on any other parties.

Section 13.12 **Further Assurance.** Each Party will duly execute and deliver, or cause to be duly executed and delivered, such further instruments and do and cause to be done such further acts and things, including the filing of such assignments, agreements, documents and instruments, as may be necessary or as the other Party may reasonably request in connection with this Agreement or to carry out more effectively the provisions and purposes, or to better assure and confirm unto such other Party its rights and remedies under this Agreement.

Section 13.13 **References.** Unless otherwise specified, (a) references in this Agreement to any Article, Section, Schedule or Exhibit will mean references to such Article, Section, Schedule or Exhibit of this Agreement, (b) references in any section to any clause are references to such clause of such section, and (c) references to any agreement, instrument or other document in this Agreement refer to such agreement, instrument or other document as originally executed or, if subsequently varied, replaced or supplemented from time to time, as so varied, replaced or supplemented and in effect at the relevant time of reference thereto.

Section 13.14 **Construction.** Except where the context otherwise requires, wherever used, the singular will include the plural, the plural the singular, the use of any gender will be applicable to all genders and the word “or” is used in the inclusive sense (and/or). The captions of this Agreement are for convenience of reference only and in no way define, describe, extend or limit the scope or intent of this Agreement or the intent of any provision contained in this Agreement. The term “including” as used herein will mean including, without limiting the generality of any description preceding such term. The language of this Agreement will be deemed to be the

language mutually chosen by the Parties and no rule of strict construction will be applied against either Party hereto. Appendices to this Agreement, or added hereto according to the terms of this Agreement, are made part of this Agreement.

Section 13.15 **Dispute Resolution Regarding Diligence.**

13.15.1 General. The Parties will negotiate in good faith and use reasonable efforts to settle any dispute, controversy or claim arising regarding whether (i) OncoGenex has satisfied its diligence obligations under Section 4.4 of this Agreement or (ii) in the event of an OncoGenex Mandate, Isis has refused to remove the applicable infringement using commercially appropriate steps, by first referring such dispute to the Chief Executive Officers of each of the Parties (or their respective designees) who will use their good faith efforts to mutually agree upon the resolution of the dispute. If any dispute is not resolved by the Chief Executive Officers of the Parties (or their designees) within 30 days after such dispute is referred to them, and a Party wishes to pursue the matter, each such dispute, controversy or claim will be finally resolved by binding arbitration in accordance with the Commercial Arbitration Rules of the American Arbitration Association (“AAA”), and judgment on the arbitration award may be entered in any court having jurisdiction thereof. The arbitration will be conducted by a panel of three persons experienced in the pharmaceutical business: within 30 days after initiation of arbitration, each party will select one person to act as arbitrator and the two party-selected arbitrators will select a third arbitrator within 30 days of their appointment. If the arbitrators selected by the parties are unable or fail to agree upon the third arbitrator, the third arbitrator will be appointed by the AAA. No individual shall be appointed to arbitrate a dispute pursuant to this Agreement unless he or she agrees in writing to be bound by the provisions of this Section 13.15. The place of arbitration will be Seattle, Washington. Either Party may apply to the arbitrators for interim injunctive relief until the arbitration award is rendered or the controversy is otherwise resolved.

13.15.2 Expenses. Except as expressly provided herein, each Party will bear its own costs and expenses and attorneys’ fees and an equal share of the arbitrators’ and any administrative fees of arbitration. The arbitrators shall have the authority to grant specific performance and to allocate between the Parties the costs of arbitration in such equitable manner as they determine. Notwithstanding the foregoing, if a Party has been found to be in material breach of this Agreement, the defaulting Party will be responsible for both Parties’ costs and expenses (including the costs of the arbitrators and any administrative fees of arbitration) and the reasonable attorneys’ fees of the non-defaulting Party.

13.15.3 Procedure. Except to the extent necessary to confirm an award or as may be required by law, neither a Party nor an arbitrator may disclose the existence, content, or results of an arbitration without the prior written consent of both Parties. In no event will an arbitration be initiated after the date when commencement of a legal or equitable proceeding based on the dispute, controversy or claim would be barred by the applicable Province of British Columbia statute of limitations.

13.15.4 Speedy Resolution. The Parties intend, and shall take all reasonable action as is necessary or desirable to ensure, that there be a speedy resolution to any dispute which becomes the subject of arbitration, and the arbitrators shall conduct the arbitration so as to resolve the dispute as expeditiously as possible.

13.15.5 Awards. All awards shall be in writing and shall state reasons. Executed copies of all awards shall be delivered by the arbitrators to the Parties as soon as is reasonably possible. All awards of the arbitrators shall be final and binding on the Parties, and there shall be no appeal of any such award whatsoever. The Parties undertake to satisfy any award without delay.

13.15.6 Except as otherwise specified in the first sentence of Section 13.15.1, no other disputes, controversies or claims shall be subject to this Section 13.15.

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IN WITNESS WHEREOF, the Parties hereto have caused this Agreement to be executed by their duly authorized representatives as of the date first above written.

ONCOGENEX TECHNOLOGIES INC.	**ISIS PHARMACEUTICALS, INC.**
Per: /s/ Scott Cormack	Per: /s/ B. Lynne Parshall
Scott D. Cormack, President & CEO	B. Lynne Parshall COO and CFO

APPENDIX A

Definitions

"Affiliate" of a party means any other party that, directly or indirectly, through one or more intermediaries, controls, is controlled by, or is under common control with such first party. For purposes of this definition only, "control" and, with correlative meanings, the terms "controlled by" and "under common control with" will mean (a) the possession, directly or indirectly, of the power to direct the management or policies of a party, whether through the ownership of voting securities or by contract relating to voting rights or corporate governance, and (b) the ownership, directly or indirectly, of more than fifty percent (50%) of the voting securities or other ownership interest of a party; provided that, if local law restricts foreign ownership, control will be established by direct or indirect ownership of the maximum ownership percentage that may, under such local law, be owned by foreign interests. In addition, Regulus Therapeutics, LLC will not be considered an Affiliate of Isis.

"Applicable Law" means the applicable laws, rules, and regulations, including any rules, regulations, guidelines, or other requirements of the Regulatory Authorities, that may be in effect from time to time.

"ASO" means an antisense oligonucleotide compound (reverse of the sense strand messenger RNA), or analog, mimic or mimetic thereof, having a sequence that is at least 6 bases long and that modulates expression of a gene target via the binding, partially or wholly, of such compound to a mRNA or pre-mRNA of such gene target.

"Business Day" means any day, other than Saturday, Sunday or any statutory holiday in the Province of British Columbia or the United States.

"Calendar Year" means each successive period of 12 months commencing on January 1 and ending on December 31.

"Clusterin" means the gene target, official symbol CLU, which is also referred to as Testosterone Repressed Prostatic Message -2 (TRPM-2), and Sulphated Glycoprotein-2 (SGP-2).

"Commercialization Agreement" has the meaning set forth in 6.2.2.

"Commercially Reasonable Efforts" means, with respect to the research, development, manufacture, release or commercialization of the Product, efforts and resources commonly used in the biotechnology industry for products of similar commercial potential at a similar stage in its lifecycle, taking into consideration their safety and efficacy, cost to develop, priority in relation to other products under development by the other Party, the competitiveness of alternative products, proprietary position, the likelihood of regulatory approval, profitability, and all other relevant factors.

"Competing Product" means a product containing an ASO that (i) acts predominantly by [***] Clusterin [***] or that is [***] Clusterin [***] (ii) [***] covered by a Valid Claim within the Product-Specific Technology Patents in the relevant country, but for the expiration, invalidity, revocation or unenforceability of such Product-Specific Technology Patents (such invalidity, revocation or unenforceability as determined by a decision of a court or other governmental agency of competent jurisdiction, unappealable or unappealed), and (iii) [***] by a Valid Claim within the Isis Core Technology Patents in the relevant country.

"Confidential Information" means all information and know-how and any tangible embodiments thereof provided by or on behalf of one Party to the other Party either in connection with the discussions and negotiations pertaining to this Agreement or in the course of performing this Agreement, including data; knowledge; practices; processes; ideas; research plans; engineering designs and drawings; research data; manufacturing processes and techniques; scientific, manufacturing, marketing and business plans; and financial and personnel matters relating to the disclosing Party or to its present or future products, sales, suppliers, customers, employees, investors or business. For purposes of this Agreement, notwithstanding the Party that disclosed such information or know-how, all information or know-how of OncoGenex will be Confidential Information of OncoGenex, and all information and know-how of Isis will be Confidential Information of Isis.

Notwithstanding the foregoing, information or know-how of a Party will not be deemed Confidential Information for purposes of this Agreement if such information or know-how:

(a) was already known to the receiving Party, other than under an obligation of confidentiality or non-use, at the time of disclosure to such receiving Party;

(b) was generally available or known to parties reasonably skilled in the field to which such information or know-how pertains, or was otherwise part of the public domain, at the time of its disclosure to, or, with respect to know-how, discovery or development by, such receiving Party;

(c) became generally available or known to parties reasonably skilled in the field to which such information or know-how pertains, or otherwise became part of the public domain, after its disclosure to such receiving Party through no fault of the receiving Party;

(d) was disclosed to such receiving Party, other than under an obligation of confidentiality or non-use, by a Third Party who had no obligation to the Party that Controls such information and know-how not to disclose such information or know-how to others; or

(e) was independently discovered or developed prior to disclosure by such receiving Party, as evidenced by their written records, without the use of Confidential Information belonging to the Party that Controls such information and know-how.

Specific aspects or details of Confidential Information will not be deemed to be within the public domain or in the possession of a Party merely because the Confidential Information is embraced by more general information in the public domain or in the possession of such Party. Further, any combination of Confidential Information will not be considered to be in the public domain or in the possession of a Party merely because individual elements of such Confidential Information are in the public domain or in the possession of such Party unless the combination and its principles are in the public domain or in the possession of such Party.

"Control" means, with respect to any Patent or other intellectual property right, possession of the right (whether by ownership, license or otherwise), to assign, transfer, or grant a license, sublicense or other right to or under, such Patent or right as provided for herein without violating the terms of any agreement or other arrangement with any Third Party.

"Discontinuance" means OncoGenex voluntarily elects to abandon [***] developing OGX-011 and/or Products, as evidenced by a written communication from an authorized officer of OncoGenex to Isis.

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

"FTE" means the equivalent of the work of one employee full time for one year (consisting of at least a total of 45.5 weeks or 1,820 hours per year (excluding vacations and holidays) of work on or directly related to the Agreement), carried out by an Isis employee. The FTE rate will be (i) [***] (U.S.) per FTE for any of the following activities: drug substance manufacturing; analytical chemistry; process chemistry; formulation; raw material ordering and handling; quality control; or manufacturing technology transfer; and (ii) [***] (U.S.) per FTE for any of the following activities: toxicology; pharmacokinetics/metabolism; regulatory; clinical development; or data management. These FTE rates will be adjusted upward on a Calendar Year basis commencing January 1, 2009 (and on January 1 of each year thereafter during the Term of this Agreement) by a factor which reflects [***] for [***] during the Term of the Agreement when compared to the [***] in the preceding year.

"GAAP" means generally accepted accounting principles of the United States consistently applied.

"Generic Product(s)" means a product or products containing an active ingredient having the same or substantially the same chemical structure as the applicable ASO targeting Clusterin that is the active ingredient contained in the applicable Product, whether approved under an NDA, ANDA, an application under 505(b)(2), or any equivalent thereof, or otherwise by a Regulatory Authority within the applicable country.

[***] means [***], a biotech company with head office in [***].

[***]

[***] means those patents listed in Appendix B.

"Improvements" means any enhancement or improvement (in each case, whether or not patented or patentable) to the Isis Core Technology or the Isis Manufacturing Technology.

"Isis Core Technology" means any discovery, invention, composition, method, process, procedure, data, information, know-how or other technology (in each case, whether or not patented or patentable) that is Controlled by Isis as of the Amendment Effective Date and that either (i) was not conceived, discovered, developed or otherwise made under or in connection with the Original Collaboration Agreement, and the application of which has utility only with respect to Products, or (ii) is necessary or useful for the development or commercialization of Products, and the application of which has utility both with respect to Products and other compositions. Isis Core Technology excludes the Isis Manufacturing Technology and Product-Specific Technology.

"Isis Core Technology Patents" means Patents Controlled by Isis that claim the Isis Core Technology on the Amendment Effective Date; *provided however* that Isis Core Technology Patents excludes the Isis Manufacturing Patents and Product-Specific Technology Patents. The Isis Core Technology Patents include, but are not limited to, the patents listed on Appendix D attached hereto.

"Isis Manufacturing Patents" means Patents Controlled by Isis that claim the manufacturing production and release processes (a) that were used to manufacture MOE Gapmers on the Amendment Effective Date and embodied in the [***], or (b) that are Controlled by Isis on or after the Amended Effective Date and otherwise are necessary, or are required by a Regulatory Authority, to be used in the manufacture of a Product. The Isis Manufacturing Patents are listed on Appendix E attached hereto. Manufacturing for this purpose includes synthesis, purification and analysis.

"Isis Manufacturing Technology" means (a) the Isis Manufacturing Patents, (b) the Release Method, and (c) all other trade secret, know-how or other information or technology (i) that is Controlled by Isis as of the Amendment Effective Date and is applicable to the manufacture, production or release

processes for the Product and embodied in the [***] or (ii) that is Controlled by Isis after the Amendment Effective Date and otherwise is necessary, or is required by a Regulatory Authority, to be used in the manufacture of a Product.

"Isis Patent Rights" means Isis Core Technology Patents and Isis Manufacturing Patents.

"Joint Patents" means all Patents that claim, cover or disclose the Joint Technology.

"Joint Technology" means any discovery, invention, composition, method, process, procedure, data, information, trade secret, know-how or other technology (in each case, whether or not patented or patentable) which is conceived, discovered, developed or otherwise made jointly by Isis and OncoGenex (as determined in

accordance with U.S. patent law). Joint Technology excludes the Product-Specific Technology.

"MOE Gapmer" means "2´MOE Gapmers" or an antisense phosphorothioate oligonucleotide of 15-30 nucleotides wherein all of the backbone linkages are modified by adding a sulfur at the non-bridging oxygen (phosphorothioate) and a stretch of at least 10 consecutive nucleotides remain unmodified (deoxy sugars) and the remaining nucleotides contain an O´-methyl O´-ethyl substitution at the 2´ position (MOE).

"Net Sales" means the gross invoice price of the Product sold by OncoGenex and sublicensees to a Third Party which is not a sublicensee of the selling party (unless such sublicensee is the end user of the Product, in which case the amount billed therefor will be deemed to be the amount that would be billed to a Third Party in an arm's-length transaction) for sales of such Product to such end users less the following items, as allocable to such Product (if not previously deducted from the amount invoiced): (i) cash, quantity and trade discounts, credits, allowances or other price reductions for such Product given to such end user, (ii) credits, discounts, rebates, chargebacks or allowances additionally granted (A) upon returns, rejections or recalls (except where any such recall arises out of the Party or its sublicensee's gross negligence, willful misconduct or fraud) or (B) for nonconforming, damaged, out-dated and returned Product, (iii) freight, shipping and insurance charges, (iv) taxes, duties, tariffs, surcharges or other governmental charges (other than income taxes), (v) government mandated rebates, and (vi) a reasonable allowance for uncollectible or bad debts determined in accordance with generally accepted accounting principles consistently applied.

"Nonexclusive Clusterin ASO" has the meaning set forth in Section 12.2.2.

"Non-Royalty Revenue" means all Revenue received by OncoGenex with the exception of Royalty Revenue and OncoGenex Direct Sales.

[***]

[***]

[***]

"OGX-011" means an antisense inhibitor of Clusterin having the sequence [***] where underlined residues are 2'-methoxyethylnucleosides (MOE) and phosphorothioate linkages throughout, also referred to as OGX-011 or ISIS 112989.

"OncoGenex Direct Sales" means Net Sales made by OncoGenex to a Third Party which is not a sublicensee of OncoGenex.

"OncoGenex Patent Rights" means any Patents Controlled by OncoGenex.

"OncoGenex Technology" means any discovery, invention, composition, method, process, procedure, data, information, trade secret, know-how or other technology (in each case, whether or not patented or patentable) that is Controlled by

OncoGenex and that is or relates to an ASO targeting Clusterin or a method of using an antisense inhibitor of Clusterin, or otherwise is necessary or useful for the development, manufacture, production or commercialization of Products. OncoGenex Technology excludes Product-Specific Technology.

"OncoGenex Technology Patents" means all Patents that claim, cover or disclose the OncoGenex Technology.

"Patents" will include (i) all U.S. patents and patent applications, (ii) any substitutions, divisions, continuations, continuations-in-part, reissues, renewals, registrations, confirmations, re-examinations, extensions, supplementary protection certificates and the like, and any provisional applications, of any such patents or patent applications, and (iii) any foreign or international equivalent of any of the foregoing.

"Permitted License" means a license under the Isis Core Technology Patents or the Isis Manufacturing Patents (but not under the Product-Specific Technology Patents) (i) granted by Isis to a Third Party to use ASOs solely to conduct such Third Party's own internal Research, or (ii) granted by Isis to a Third Party (provided that such Third Party is [***] and neither such Third Party nor any of its Affiliates is [***] to manufacture ASOs solely for unaffiliated third parties; *provided*, *however*, in each case, any such ASOs are not specified in such license or a related document to be ASOs (a) that act predominantly by [***] Clusterin [***] or (b) that are [***] Clusterin [***] or products containing such ASOs. For purposes of clarification, a Permitted License shall not permit Isis or its Affiliates to supply to a Third Party ASOs that act predominantly by [***] Clusterin [***] or that are [***] Clusterin [***] or products containing such ASOs.

"Product" means any pharmaceutical preparation (in intravenous, subcutaneous, oral or any other formulation) containing as the sole active pharmaceutical ingredient either (a) OGX-011, or (b) any other ASO targeting Clusterin that either (i) was identified under the Original Collaboration Agreement or (ii) is identified under Section 4.1.3. For clarity, the Product may be used in association with other products such as chemotherapy, hormone ablation therapy and radiation therapy and the immediately preceding sentence does not limit such intended use.

"Product-Specific Technology" means any discovery, invention, composition, method, process, procedure, data, information, trade secret, know-how or other technology (in each case, whether or not patented or patentable) which is conceived, discovered, developed or otherwise made solely by Isis or OncoGenex, or jointly by Isis and OncoGenex, under or in connection with the Original Collaboration Agreement or this Agreement, and the application of which has utility only with respect to Products. For purposes of clarification Product-Specific Technology excludes the Isis Manufacturing Technology and Isis Core Technology.

"Product-Specific Technology Patents" means all Patents that claim, cover or disclose Product-Specific Technology. Product-Specific Technology Patents include, but are not limited to the patents listed on Appendix G attached hereto. For purposes of clarification, any Product-Specific Technology Patents assigned to OncoGenex as set

forth in Section 4.2.1 or 8.2.2 will still be considered Product-Specific Technology Patents for determining the royalty term and applicable royalty rates under Article 6.

"**Qualified Partner"** means a corporation or other entity (a) whose primary business is the commercialization of pharmaceutical products, (b) which, on its own or in connection with a Third Party, does not operate a contract oligonucleotide manufacturing business and (c) is approved as Qualified Partner by Isis at the request of OncoGenex (or its Affiliate), such approval not to be unreasonably withheld.

"Registration Clinical 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 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 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.

"Regulatory Authority" means any applicable government entities regulating or otherwise exercising authority with respect to the development and commercialization of the Product.

"Regulatory Documentation" means all applications, registrations, licenses, authorizations and approvals (including all regulatory approvals), all correspondence submitted to or received from Regulatory Authorities (including minutes and official contact reports relating to any communications with any Regulatory Authority), all supporting documents and all clinical studies and tests, including the manufacturing batch records, relating to the Product, and all data contained in any of the foregoing, including all regulatory drug lists, advertising and promotion documents, adverse event files and complaint files.

"Release Method" means the methods used by Isis as at the Amendment Effective Date for the release of OGX-011 utilizing liquid chromatography – mass spectrometry and specified in Specification outlined in [***].

"Research" means *in vitro* or *in vivo* research, excluding any and all uses in humans.

"Revenue" means all revenues, receipts, monies, and the fair market value of all other consideration directly or indirectly collected or received whether by way of cash or credit or any barter, benefit, advantage, or concession received OncoGenex relating to the sale, license or any other commercial transaction involving the Product, with the exception of the following: (i) any consideration received for the reimbursement for research and development activities and (ii) any consideration received for the fair market portion of any sale of equity or quasi-equity securities including, without limitation, common shares and preferred shares.

"Royalty Due Date" means March 31, June 30, September 30 and December 31 of each year during the term of this Agreement.

"Royalty Revenue" means, with respect to a Product in a country, all Revenue received by OncoGenex that is based on a percentage of Net Sales of such Product by a Third Party sublicensed to sell such Product in such country.

"**Start Date**" means November 16, 2001.

"**Supply Chain Network**" will include the names, contact information, and supply description of all providers, whether currently used or alternative preferred suppliers as of the Amendment Effective Date, and who supply modified and unmodified nucleotides, solid support and other reagents and raw materials specified in the Isis Manufacturing Technology.

"Third Party" means any party other than Isis or OncoGenex.

"Third Party Payments" means royalties, milestones, and other payments owing to Third Parties, including payments as set forth in Section 6.3 and Section 6.5

"Valid Claim" means either (a) a claim of an issued and unexpired patent included within the Isis Patent Rights, which has not been held permanently revoked, unenforceable or invalid by a decision of a court or other governmental agency of competent jurisdiction, unappealable or unappealed within the time allowed for appeal, and which has not been admitted to be invalid or unenforceable through reissue or disclaimer or otherwise or (b) a claim of a pending patent application included within the Isis Patent Rights, which was filed in good faith and has not been abandoned, finally rejected or expired without the possibility of appeal or refiling, provided however, that Valid Claim will exclude any such pending claim in an application that has not been granted within (x) [***] years following the earliest filing date for such application in the United States (unless and until such claim is granted), and (y) [***] years following the earliest filing date for such application outside of the United States (unless and until such claim is granted).

APPENDIX B

[***]

	Docket #	Country/Treaty	Patent/ Application #	Title	Issue Date
[***]					
	[***]	[***]	[***]	[***]	[***]

APPENDIX C

[***]

Assignee	Docket #	Country/Treaty	Patent/ Application #	Title	Issue Date
[***]					
	[***]	[***]	[***]	[***]	[***]

APPENDIX D

ISIS CORE TECHNOLOGY PATENTS

Assignee	Docket #	Country/Treaty	Patent/ Application #	Title	Issue Date
ISIS					
	[***]	[***]	[***]	[***]	[***]

APPENDIX E

ISIS MANUFACTURING PATENTS

Technology	Docket #	Country/Treaty	Patent/ Application #	Title	Filing Date
[***]	[***]	[***]	[***]	[***]	[***]

APPENDIX F

[***]

APPENDIX G

PRODUCT-SPECIFIC TECHNOLOGY PATENTS

Docket No.	Country	Patent/ Applicaion #	Filing Date	Issue Date	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: November 10, 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: November 10, 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 September 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: November 10, 2008

/s/ Stanley T. Crooke	/s/ B. Lynne Parshall
Stanley T. Crooke, M.D., Ph.D.	B. Lynne Parshall, J.D.
Chief Executive Officer	Chief Financial Officer

A signed original of this written statement required by Section 906 has been provided to Isis Pharmaceuticals, Inc. and will be retained by Isis Pharmaceuticals, Inc. and furnished to the Securities and Exchange Commission or its staff upon request.