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, 2011

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.)

2855 Gazelle Court, Carlsbad, CA 92010
(Address of principal executive offices, including zip code)

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

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

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

Common Stock, $.001 Par Value

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

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes 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 definition of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

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

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

The number of shares of voting common stock outstanding as of November 1, 2011 was 99,729,321.

ISIS PHARMACEUTICALS, INC.
FORM 10-Q

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TRADEMARKS

Isis Pharmaceuticals® is a registered trademark of Isis Pharmaceuticals, Inc.

Regulus Therapeutics™ is a trademark of Regulus Therapeutics Inc.

Ibis T5000™ is a trademark of Ibis Biosciences, Inc.

Vitravene® is a registered trademark of Novartis AG.

Kynamro™ is a trademark of Genzyme Corporation.

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

	September 30, 2011 (Unaudited)	December 31, 2010
ASSETS		
Current assets:		
Cash and cash equivalents	$ 55,263	$ 70,052
Short-term investments	309,500	402,301
Contracts receivable	1,858	1,242
Inventories	2,915	2,484
Other current assets	7,553	7,058

Total current assets	377,089	483,137
Property, plant and equipment, net	98,019	35,703
Licenses, net	10,562	12,288
Patents, net	16,994	15,821
Deposits and other assets	3,121	3,528
Total assets	$ 505,785	$ 550,477
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 6,653	$ 6,523
Accrued compensation	5,233	6,831
Accrued liabilities	15,071	12,389
Current portion of long-term obligations	4,157	5,645
Current portion of deferred contract revenue	52,428	74,502
Total current liabilities	83,542	105,890
Long-term deferred contract revenue	19,415	50,413
2 5/8 percent convertible subordinated notes	139,239	132,895
Long-term obligations, less current portion	4,724	5,720
Long-term financing liability for leased facility	68,895	10,147
Investment in Regulus Therapeutics Inc.	3,145	870
Total liabilities	318,960	305,935
Stockholders' equity:		
Common stock, $0.001 par value; 200,000,000 shares authorized, 99,723,317 and 99,393,780 shares issued and outstanding at September 30, 2011 and December 31, 2010, respectively	100	99
Additional paid-in capital	1,009,330	1,000,181
Accumulated other comprehensive income	(1,153)	949
Accumulated deficit	(821,452)	(756,687)
Total stockholders' equity	186,825	244,542
Total liabilities and stockholders' equity	$ 505,785	$ 550,477

See accompanying notes.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2011	2010	2011	2010
Revenue:				
Research and development revenue under collaborative agreements	$ 20,189	$ 27,785	$ 64,508	$ 77,484
Licensing and royalty revenue	524	839	2,175	4,569
Total revenue	20,713	28,624	66,683	82,053
Expenses:				
Research and development	39,924	34,716	110,178	105,827
General and administrative	3,105	2,855	8,989	8,724
Total operating expenses	43,029	37,571	119,167	114,551
Loss from operations	(22,316)	(8,947)	(52,484)	(32,498)
Other income (expense):				
Equity in net loss of Regulus Therapeutics Inc.	(386)	(930)	(2,275)	(6,358)
Investment income	575	776	1,896	2,590
Interest expense	(4,773)	(3,338)	(11,624)	(9,835)
Gain (loss) on investments, net	18	(15)	(267)	(1,162)
Loss before income tax expense	(26,882)	(12,454)	(64,754)	(47,263)
Income tax expense	—	—	(11)	(2)
Net loss	$ (26,882)	$ (12,454)	$ (64,765)	$ (47,265)
Basic and diluted net loss per share	$ (0.27)	$ (0.13)	$ (0.65)	$ (0.48)
Shares used in computing basic and diluted net loss per share	99,687	99,196	99,620	99,101

See accompanying notes.

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

	Nine Months Ended September 30,	
	2011	2010
Net cash used in operating activities	$ (90,467)	$ (38,090)
Investing activities:		
Purchases of short-term investments	(284,379)	(429,631)
Proceeds from the sale of short-term investments	371,872	483,476
Purchases of property, plant and equipment	(7,655)	(12,740)
Proceeds from land sold to BioMed	—	10,147
Reduction of cash due to deconsolidation of Regulus Therapeutics Inc. upon adoption of a new accounting standard	—	(16,228)
Acquisition of licenses and other assets	(2,544)	(3,430)
Purchases of strategic investments	(359)	(658)
Net cash provided by investing activities	76,935	30,936
Financing activities:		
Proceeds from issuance of equity	1,554	2,036
Proceeds from equipment financing arrangement	1,625	3,083
Principal payments on debt and capital lease obligations	(4,436)	(3,098)
Net cash (used in) provided by financing activities	(1,257)	2,021
Net decrease in cash and cash equivalents	(14,789)	(5,133)
Cash and cash equivalents at beginning of period	70,052	105,255
Cash and cash equivalents at end of period	$ 55,263	$ 100,122
Supplemental disclosures of cash flow information:		
Interest paid	$ 4,647	$ 4,694
Income taxes paid	$ 2	$ 7,700
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 1,378	$ 927
Capitalized costs and financing liability associated with leased facility	$ 58,748	$ —

See accompanying notes.

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ISIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
September 30, 2011
(Unaudited)

1. Basis of Presentation

The unaudited interim condensed consolidated financial statements for the three and nine month periods ended September 30, 2011 and 2010 have been prepared on the same basis as the audited financial statements for the year ended December 31, 2010. 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, 2010 included in our Annual Report on Form 10-K filed with the Securities and Exchange Commission ("SEC").

The condensed consolidated financial statements include the accounts of Isis Pharmaceuticals, Inc. ("we", "us" or "our") and our wholly owned subsidiaries, Isis USA Ltd. and Symphony GenIsis, Inc. We use the equity method of accounting to account for our investment in Regulus Therapeutics Inc.

2. Significant Accounting Policies

Revenue Recognition

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

Research and development revenue under collaborative agreements

On January 1, 2011, we adopted an accounting standard, which amended the criteria to identify separate units of accounting for revenue arrangements with multiple deliverables. The new guidance replaces the concept of allocating revenue among deliverables in a multiple-element revenue arrangement according to fair value with an allocation based on selling price. The new standard is applicable on a prospective basis to agreements we entered into or materially modified after January 1, 2011. The adoption of the standard did not impact our financial position or results of operations as of and for the nine month period ended September 30, 2011 as we did not enter into or materially modify any multiple-element arrangements during that period. However, the adoption of this standard may result in revenue recognition for future agreements that is different from our existing multiple-element arrangements.

For agreements that we entered into or materially modified prior to the adoption of the revised multiple element guidance, we recognize revenue from each element of the arrangement as long as we can determine a standalone value for the delivered element and fair value for the undelivered elements, we have completed our obligation to deliver or perform on that element and we are reasonably assured of collecting the resulting receivable.

We often enter into collaborations with multiple deliverables under which we receive non-refundable upfront payments. For collaborations where we determine that there is a single unit of accounting, we recognize revenue related to upfront payments ratably over our estimated period of performance relating to the term of the contractual arrangements. Occasionally, we must estimate our period of performance when the agreements we entered into do not clearly define such information. Our collaborative agreements typically include a research and/or development project plan that includes the activities the agreement requires each party to perform during the collaboration and the party responsible for performing them. We estimate the period of time over which we will complete the activities for which we are responsible and use that period of time as our period of performance for purposes of revenue recognition and amortize revenue over such period. If our collaborators ask us to continue performing work in a collaboration beyond the initial period of performance, we extend our amortization period to correspond to the new extended period of performance. The revenue we recognize could be materially different if different estimates prevail. We have made estimates of our continuing obligations on several agreements. Adjustments to performance periods and related adjustments to revenue amortization periods have had a material impact on our revenue on only one occasion. When Alnylam Pharmaceuticals, Inc. terminated the companies' single-stranded RNAi, or ssRNAi, research program in November 2010, we recognized as revenue $4.9 million, which was the remaining deferred revenue from the upfront fee that we were amortizing into revenue over the research term.

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As part of our Genzyme strategic alliance, in February 2008 Genzyme made a $150 million equity investment in us by purchasing five million shares of our common stock at $30 per share. The price Genzyme paid for our common stock represented a significant premium over the fair value of our stock. We accounted for this premium as deferred revenue and are amortizing it along with the $175 million licensing fee that we received in June 2008 ratably into revenue until June 2012, which represents the end of our performance obligation based on the current research and development plan.

Our collaborations often include contractual milestones, which typically relate to the achievement of pre-specified development, regulatory and commercialization events. These three categories of milestone events reflect the three stages of the life-cycle of our drugs, which we describe in more detail in the following paragraph.

Prior to the first stage in the life-cycle of our drugs, we perform a significant amount of work using our proprietary antisense technology to design chemical compounds which interact with specific genes that are good targets for drug discovery. From these research efforts, we hope to identify a development candidate. The designation of a development candidate is the first stage in the life-cycle of our drugs. A development candidate is a chemical compound that has demonstrated the necessary safety and efficacy in preclinical animal studies to warrant further study in humans. During the first step of the development stage, we or our partners study our drugs in IND-enabling studies, which are animal studies intended to support an Investigational New Drug, or IND, application and/or the foreign equivalent. An approved IND allows us or our partners to study our development candidate in humans. If the regulatory agency approves the IND, we or our partners initiate Phase 1 clinical trials in which we typically enroll a small number of healthy volunteers to ensure the development candidate is safe for use in patients. If we or our partners determine that a development candidate is safe based on the Phase 1 data, we or our partners initiate Phase 2 studies that are generally larger scale studies in patients with the primary intent of determining the efficacy of the development candidate. The final step in the development stage is Phase 3 studies to gather the necessary safety and efficacy data to request marketing approval from the Food and Drug Administration, or FDA, and/or foreign equivalents. The Phase 3 studies typically involve large numbers of patients and can take up to several years to complete. If the data gathered during the trials demonstrates acceptable safety and efficacy results, we or our partner will submit an application to the FDA or its foreign equivalents for marketing approval. This stage of the drug's life-cycle is the regulatory stage. If a drug achieves marketing approval, it moves into the commercialization stage, during which our partner will market and sell the drug to patients. Although our partner will ultimately be responsible for marketing and selling the drug, our efforts to discover and develop a drug that is safe, effective and reliable contributes significantly to our partner's ability to successfully sell the drug. The FDA and its foreign equivalents have the authority to impose significant restrictions on an approved drug through the product label and on advertising, promotional and distribution activities. Therefore, our efforts designing and executing the necessary animal and human studies are critical to obtaining claims in the product label from the regulatory agencies that would allow our partner to successfully commercialize our drug. Further, the patent protection afforded our drugs as a result of our initial patent applications and related prosecution activities in the United States and foreign jurisdictions are critical to our partner's ability to sell our drugs without competition from generic drugs. The potential sales volume of an approved drug is dependent on several factors including the size of the patient population, market penetration of the drug, and the price charged for the drug.

Generally, the milestone events contained in our partnership agreements coincide with the progression of our drugs from development, to regulatory approval and then to commercialization. The process of successfully discovering a new development candidate, having it approved and ultimately sold for a profit is highly uncertain. As such, the milestone payments we may earn from our partners involve a significant degree of risk to achieve. Therefore, as a drug progresses through the stages of its life-cycle, the value of the drug generally increases.

Development milestones in our partnerships may include the following types of events:

- Designation of a development candidate. Following the designation of a development candidate, IND-enabling animal studies for a new development candidate generally take 12 to 18 months to complete;
- Initiation of a Phase 1 clinical trial. Generally, Phase 1 clinical trials take one to two years to complete;
- Initiation or completion of a Phase 2 clinical trial. Generally, Phase 2 clinical trials take one to three years to complete;
- Initiation or completion of a Phase 3 clinical trial. Generally, Phase 3 clinical trials take two to four years to complete.

Regulatory milestones in our partnerships may include the following types of events:

- Filing of regulatory applications for marketing approval such as a New Drug Application, or NDA, in the United States or Marketing Authorization Application in Europe. Generally, it takes six to twelve months to prepare and submit regulatory filings.
- Marketing approval in a major market, such as the United States, Europe or Japan. Generally it takes one to two years after an application is submitted to obtain approval from the applicable regulatory agency.

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Commercialization milestones in our partnerships may include the following types of events:

- First commercial sale in a particular market, such as in the United States or Europe.
- Product sales in excess of a pre-specified threshold, such as annual sales exceeding $1 billion. The amount of time to achieve this type of milestone depends on several factors including but not limited to the dollar amount of the threshold, the pricing of the product and the pace at which customers begin using the product.

We assess whether a substantive milestone exists at the inception of our agreements. When a substantive milestone is achieved, we recognize revenue related to the milestone payment. For our existing licensing and collaboration agreements in which we are involved in the discovery and/or development of the related drug or provide the partner with ongoing access to new technologies we discover, we determined that all future development, regulatory and commercialization milestones are substantive. For example, for our strategic alliance with GSK we are using our antisense drug discovery platform to seek out and develop new drugs against targets for rare and serious diseases. Alternatively, we provide on-going access to our technology to Alnylam to develop and commercialize RNA interference, or RNAi, therapeutics. We consider milestones for both of these collaborations to be substantive. For those agreements that do not meet the following criteria, we do not consider the future milestones to be substantive. In evaluating if a milestone is substantive we consider whether:

- Substantive uncertainty exists as to the achievement of the milestone event at the inception of the arrangement;
- The achievement of the milestone involves substantive effort and can only be achieved based in whole or part on our performance or the occurrence of a specific outcome resulting from our performance;
- The amount of the milestone payment appears reasonable either in relation to the effort expended or to the enhancement of the value of the delivered items;
- There is no future performance required to earn the milestone; and
- The consideration is reasonable relative to all deliverables and payment terms in the arrangement.

If any of these conditions are not met, we will defer recognition of the milestone payment and recognize it as revenue over the estimated period of performance, if any. In May 2011, we initiated a Phase 1 clinical study on ISIS-TTR$_{Rx}$, the first drug selected as part of our collaboration with GlaxoSmithKline, or GSK, and in January 2011 OncoGenex Pharmaceuticals Inc., initiated a Phase 2 trial of OGX-427 in men with metastatic prostate cancer. We considered the initiation of Phase 1 and Phase 2 clinical trials to be substantive milestones because the level of effort and inherent risk associated with successfully moving a drug into Phase 1 and Phase 2 clinical development is high. Therefore, we recognized the entire $5 million milestone payment from GSK in the second quarter of 2011 and the entire $750,000 milestone payment from OncoGenex in the first quarter of 2011. Further information about our collaborative arrangements can be found below in Note 6, *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 significant future performance obligations and are reasonably assured of collecting the resulting receivable.

Short-term investments

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

We have equity investments in privately- and publicly-held biotechnology companies that we have received as part of a technology license or collaboration agreement. We hold ownership interests of less than 20 percent in each of the respective companies except Regulus, our jointly owned subsidiary. In determining if and when a decrease in market value below our cost in our equity positions is temporary or other-than-temporary, we examine historical trends in the stock price, the financial condition of the company, near term prospects of the company and our current need for cash. We record unrealized gains and losses related to temporary declines in the publicly-held companies as a separate component of stockholders’ equity and account for securities in the privately-held companies, except for Regulus, under the cost method of accounting because we own less than 20 percent and do not have significant influence in their operations. Most of the cost method investments we hold are in early stage biotechnology companies and realization of our equity position in those companies is uncertain. In those circumstances we record a full valuation allowance. When we determine that a decline in value in either a public or private investment is other-than-temporary, we recognize an impairment loss in the period in which the other-than-temporary decline occurs.

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Inventory valuation

We capitalize the costs of raw materials that we purchase for use in producing our drugs because until we use these raw materials they have alternative future uses. We include in inventory raw material costs for drugs that we manufacture for our partners under contractual terms and that we use primarily in our clinical development activities and drug products. We can use each of our raw materials in multiple products and, as a result, each raw material has future economic value independent of the development status of any single drug. For example, if one of our drugs failed, we could use the raw materials allocated for that drug to manufacture our other drugs. We expense these costs when we deliver the drugs to our partners, or as we provide these drugs for our own clinical trials. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. We review inventory periodically and reduce the carrying value of items we consider to be slow moving or obsolete to their estimated net realizable value. We consider several factors in 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-off for the first nine months of 2011 and 2010. Total inventory, which consisted of raw materials, was $2.9 million and $2.5 million as of September 30, 2011 and December 31, 2010, respectively.

Patents

We capitalize costs consisting principally of outside legal costs and filing fees related to obtaining patents. We review our capitalized patent costs regularly to ensure that they include costs for patents and patent applications that have future value. We evaluate patents and patent applications that we are not actively pursuing and write off any associated costs. We amortize patent costs over their estimated useful lives of 10 years, beginning with the date the United States Patent and Trademark Office, or foreign equivalent, issues the patent. For the first nine months of 2011 and 2010, we recorded a non-cash charge of $883,000 and $1.0 million, respectively, which we included in research and development expenses, related to the write-down of our patent costs to their estimated net realizable values.

Long-lived assets

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

Equity method of accounting

We account for our ownership interest in Regulus using the equity method of accounting. We include our share of Regulus' operating results on a separate line in our condensed consolidated statement of operations called "Equity in net loss of Regulus Therapeutics Inc." On our condensed consolidated balance sheet, we present our investment in Regulus on a separate line in the non-current liabilities section called "Investment in Regulus Therapeutics Inc." Under the equity method of accounting, we are required to suspend recognizing losses if the carrying amount of our investment in Regulus exceeds the amount of funding we are required to provide to Regulus. Since we and Alnylam are guarantors of both of the convertible notes that Regulus issued to GSK we will continue to recognize losses in excess of our net investment in Regulus up to the principal plus accrued interest we guaranteed, which was $5.4 million at September 30, 2011.

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. Adjustments to our estimates have had a material impact to our actual results on only one occasion. When Alnylam terminated the ssRNAi research program in November 2010, we recognized as revenue $4.9 million, which was the remaining deferred revenue from the upfront fee that we were amortizing into revenue over the research term.

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Basic and diluted net loss per share

We compute basic net loss per share by dividing the net loss by the weighted-average number of common shares outstanding during the period. As we incurred a loss from continuing operations for the three and nine months ended September 30, 2011 and 2010, we did not include the following diluted common equivalent shares in the computation of diluted net loss from continuing operations per share because the effect would have been anti-dilutive:

- $2^5/_8$ percent convertible subordinated notes;
- GlaxoSmithKline convertible promissory notes; and
- Dilutive stock options

Consolidation of variable interest entities

We identify entities as variable interest entities either: (1) that do not have sufficient equity investment at risk to permit the entity to finance its activities without additional subordinated financial support, or (2) in which the equity investors lack an essential characteristic of a controlling financial interest. We perform ongoing qualitative assessments of our variable interest entities to determine whether we have a controlling financial interest in the variable interest entity and therefore are the primary beneficiary. As of September 30, 2011 and December 31, 2010, we had collaborative arrangements with eight entities that we consider to be variable interest entities. We are not the primary beneficiary for any of these entities as we do not have both the power to direct the activities that most significantly impact the economic performance of our variable interest entities and the obligation to absorb losses or right to receive benefits from our variable interest entities that could potentially be significant to the variable interest entities. In the case of Regulus, since we and Alnylam share the ability to impact Regulus' economic performance, we are not the primary beneficiary of Regulus.

Comprehensive loss

We report, in addition to net loss, comprehensive loss and its components as follows (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2011	2010	2011	2010
Comprehensive loss:				

Unrealized holding gains (losses)	$ (1,552)	$ 221	$ (2,102)	$ (66)
Reclassification adjustment for realized loss included in net loss	—	—	—	(925)
Net loss	(26,882)	(12,454)	(64,765)	(47,265)
Comprehensive loss	$ (28,434)	$ (12,233)	$ (66,867)	$ (48,256)

Convertible debt

We account for our $2^5/_8$ percent convertible notes by separating the liability and equity components of the instruments in a manner that reflects our nonconvertible debt borrowing rate when we recognize interest expense in subsequent periods. As a result, we assigned a value to the debt component of our $2^5/_8$ percent convertible notes equal to the estimated fair value of a similar debt instrument without the conversion feature, which resulted in us recording the debt at a discount. We are amortizing the resulting debt discount over the life of the debt as additional non-cash interest expense utilizing the effective interest method.

Segment information

Prior to 2011 we reported our results in two separate segments; Drug Discovery and Development and Regulus. Beginning in the first quarter of 2011, we no longer consider Regulus as an operating segment because our chief decision making officer no longer reviews Regulus' operating results for purposes of making resource allocations. Therefore we only provide financial information and results for our Drug Discovery and Development operations.

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Stock-based compensation expense

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

For the nine months ended September 30, 2011 and 2010, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Nine Months Ended September 30,	
	2011	2010
Risk-free interest rate	2.3%	2.8%
Dividend yield	0.0%	0.0%
Volatility	52.4%	55.7%
Expected Life	5.3 years	5.2 years

Board of Director Stock Options:

	Nine Months Ended September 30,	
	2011	2010
Risk-free interest rate	2.9%	2.7%
Dividend yield	0.0%	0.0%
Volatility	52.8%	57.7%
Expected Life	7.8 years	7.8 years

ESPP:

	Nine Months Ended September 30,	
	2011	2010
Risk-free interest rate	0.1%	0.2%
Dividend yield	0.0%	0.0%
Volatility	34.9%	47.8%
Expected Life	6 months	6 months

The following table summarizes stock-based compensation expense related to employee and non-employee stock options and the ESPP for the three and nine months ended September 30, 2011 and 2010 (in thousands), which was allocated as follows:

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2011	2010	2011	2010
Research and development	$ 2,017	$ 2,476	$ 6,594	$ 7,912
General and administrative	347	484	1,002	1,535
Total	$ 2,364	$ 2,960	$ 7,596	$ 9,447

As of September 30, 2011, total unrecognized compensation cost related to non-vested stock-based compensation plans was $9.7 million. We will adjust total unrecognized compensation cost for future changes in estimated forfeitures. We expect to recognize this cost over a weighted average period of 1.3 years.

Impact of recently issued accounting standards

In June 2011, the FASB amended its authoritative guidance on the presentation of comprehensive income. Under the amendment, companies have the option to present the components of net income and other comprehensive income either in a single continuous statement of comprehensive income or in separate but consecutive statements. This amendment eliminates the currently available option to present the components of other comprehensive income as part of the statement of changes in stockholders' equity. The amendment does not change the items that must be reported in other comprehensive income or when an item of other comprehensive income must be reclassified to net income. The guidance is effective retrospectively for fiscal years, and interim periods within those years, beginning after December 15, 2011 and is effective for our fiscal year beginning January 1, 2012. As this guidance relates to presentation only, the adoption of this guidance will not have any other effect on our financial statements.

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3. Investments

As of September 30, 2011, our excess cash was primarily invested in debt instruments and commercial paper with strong credit ratings of financial institutions, corporations, U.S. government agencies and the U.S. Treasury with an investment grade rating at or above A-1, P-1 or F-1 by Moody's, Standard & Poor's (S&P) or Fitch, respectively. We have established guidelines relative to diversification and maturities that maintain safety and liquidity. We periodically review and modify these guidelines to maximize trends in yields and interest rates without compromising safety and liquidity.

The following table summarizes the contract maturity of the available-for-sale securities we held as of September 30, 2011:

One year or less	76%
After one year but within two years	20%
After two years but within three years	4%
Total	100%

In April 2011, S&P affirmed the 'AAA/A-1+' rating on the sovereign credit rating of the United States. At the same time, however, S&P lowered the outlook of the long-term rating to 'Negative' from 'Stable.' In July 2011 Moody's placed the AAA bond rating for the United States on review for a possible downgrade. The actions taken by S&P and Moody's pertain primarily to the long-term challenges associated with the United States' budget deficits and rising indebtedness. As illustrated above, our excess cash is invested primarily in short-term instruments with 96 percent of our available-for-sale securities having a maturity of less than two years. Therefore, we do not believe the action taken by S&P and Moody's impact the carrying value of our available-for-sale securities at September 30, 2011.

At September 30, 2011, we had an ownership interest of less than 20 percent in each of five private companies and two public companies with which we conduct business. The companies are Santaris Pharma A/S (formerly Pantheco A/S), Achaogen, Inc., Atlantic Pharmaceuticals Limited, Altair Therapeutics Inc. and Excaliard Pharmaceuticals, Inc., which are privately-held and Antisense Therapeutics Limited, or ATL, and iCo Therapeutics Inc., which are publicly-traded. We account for securities in the privately-held companies under the cost method of accounting and we classify the securities in the publicly-traded companies as available-for-sale. During the first nine months of 2011, we recognized a $267,000 loss on investments primarily consisting of a $359,000 valuation allowance we recorded related to the investment we made in Excaliard in February 2011. Because realization of our Excaliard investment is uncertain we recorded a full valuation allowance.

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The following is a summary of our investments (in thousands):

September 30, 2011	Amortized Cost	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Short-term investments:					
Corporate debt securities	$ 149,296	$ 28	$ (380)	$ —	$ 148,944
Debt securities issued by U.S. government agencies	65,707	22	(9)	—	65,720
Debt securities issued by the U.S. Treasury	4,506	6	—	—	4,512
Debt securities issued by states of the United States and political subdivisions of the states	15,451	3	—	—	15,454
Total securities with a maturity of one year or less	234,960	59	(389)	—	234,630
Corporate debt securities	59,430	35	(412)	—	59,053
Debt securities issued by U.S. government agencies	12,263	6	(157)	—	12,112
Debt securities issued by states of the United States and political subdivisions of the states	3,706	1	(2)	—	3,705
Total securities with a maturity of more than one year	75,399	42	(571)	—	74,870
Subtotal	$ 310,359	$ 101	$ (960)	$ —	$ 309,500
Equity securities:					
Current portion (included in Other current assets)	$ 1,538	$ 511	$ —	$ (880)	$ 1,169
Long-term portion (included in Deposits and other assets)	625	—	—	—	625
Subtotal	$ 2,163	$ 511	$ —	$ (880)	$ 1,794
	$ 312,522	$ 612	$ (960)	$ (880)	$ 311,294

December 31, 2010	Amortized Cost	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Short-term investments:					
Corporate debt securities	$ 196,010	$ 294	$ (41)	$ —	$ 196,263
Debt securities issued by U.S. government agencies	119,890	53	(34)	—	119,909
Debt securities issued by the U.S. Treasury	24,030	10	—	—	24,040
Debt securities issued by states of the United States and political subdivisions of the states	6,989	3	—	—	6,992
Total securities with a maturity of one year or less	346,919	360	(75)	—	347,204
Corporate debt securities	47,842	167	(44)	—	47,965
Debt securities issued by U.S. government agencies	7,139	4	(11)	—	7,132
Total securities with a maturity of more than one year	54,981	171	(55)	—	55,097
Subtotal	$ 401,900	$ 531	$ (130)	$ —	$ 402,301
Equity securities:					
Current portion (included in Other current assets)	$ 1,538	$ 1,353	$ —	$ (880)	$ 2,011
Long-term portion (included in Deposits and other assets)	625	—	—	—	625
Subtotal	$ 2,163	$ 1,353	$ —	$ (880)	$ 2,636
	$ 404,063	$ 1,884	$ (130)	$ (880)	$ 404,937

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Investments we consider to be temporarily impaired at September 30, 2011 are as follows (in thousands):

		Less than 12 months of temporary impairment	
	Number of Investments	Estimated Fair Value	Unrealized Losses
Corporate debt securities	66	$ 137,205	$ (792)
Debt securities issued by U.S. government agencies	9	28,565	(166)
Debt securities issued by states of the United States and political subdivisions of the states	2	2,405	(2)
Total temporarily impaired securities	77	$ 168,175	$ (960)

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

4. Fair Value Measurements

We use a three-tier fair value hierarchy to prioritize the inputs used in our fair value measurements. These tiers include: Level 1, defined as observable inputs such as quoted prices in active markets, which includes our money market funds and treasury securities classified as available-for-sale securities and equity securities in publicly-held biotechnology companies; Level 2, defined as inputs other than quoted prices in active markets that are either directly or indirectly observable, which includes our fixed income securities and commercial paper classified as available-for-sale securities; and Level 3, defined as unobservable inputs in which little or no market data exists, therefore requiring an entity to develop its own assumptions. To estimate the fair value of securities classified as Level 2, we utilize the services of a fixed income pricing provider that uses an industry standard valuation model, which is based on a market approach. The significant inputs for the valuation model include reported trades, broker/dealer quotes, benchmark securities and bids. At September 30, 2011, we had no securities that we classified as Level 3.

Below is a table of our assets that we measure at fair value on a recurring basis. For the following major security types, we break down the inputs used to measure fair value at September 30, 2011 (in thousands):

	Total	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 55,239	$ 48,073	$ 7,166	$ —
Corporate debt securities (2)	207,997	—	207,997	—
Debt securities issued by U.S. government agencies (2)	77,832	—	77,832	—
Debt securities issued by the U.S. Treasury (2)	4,512	4,512	—	—
Debt securities issued by states of the United States and political subdivisions of the states (2)	19,159	—	19,159	—
Equity securities (3)	1,169	1,169	—	—
Total	$ 365,908	$ 53,754	$ 312,154	$ —

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

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

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

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5. New Facility

The leases on our former primary research and development facilities expire at the end of 2011. Rather than invest in costly renovations to these facilities, we chose to consolidate the majority of our operations in a new leased facility that Biomed Realty Trust, Inc. constructed. To make our move, which was completed in August 2011, as efficient as possible, we requested access to the new facility prior to the completion of construction. To gain early access, in May 2011, we agreed to modify our lease with BioMed to accept additional responsibility. As a result, we recorded the costs for the facility as a fixed asset, which at September 30, 2011 was $58.8 million. We also recorded a corresponding liability. This amount is in addition to the $10.1 million we recorded in 2010 for the cost of the land. In the third quarter of 2011, we began depreciating the cost of the facility over its economic useful life. Our rent payments begin on January 1, 2012 and will decrease the liability over the term of the lease.

6. Collaborative Arrangements and Licensing Agreements

Traditional Pharmaceutical Alliances and Licensing

GlaxoSmithKline

In March 2010, we entered into a strategic alliance with GSK, which covers up to six programs, in which we use our antisense drug discovery platform to seek out and develop new drugs against targets for rare and serious diseases, including infectious diseases and some conditions causing blindness. This alliance allows us to control and facilitate rapid development of drugs while still being eligible to receive milestone payments as we advance these drugs in clinical development.

As of September 30, 2011, we have received $48 million from GSK, which includes the $35 million upfront payment and the $3 million payment we received in May 2011 when GSK expanded the collaboration by initiating a sixth program, both of which we are amortizing over the five year period of our performance. To date we have earned $15 million in milestone payments, including a $5 million milestone that we will recognize in the fourth quarter of 2011 for designation of ISIS-AAT$_{Rx}$ as the second development candidate in our collaboration with GSK.

We are also eligible to receive on average up to $20 million in milestone payments per program up to Phase 2 proof-of-concept. GSK has the option to license drugs from these programs at Phase 2 proof-of-concept, and will be responsible for all further development and commercialization. If all six programs are successfully developed for one or more indications and commercialized through pre-agreed sales targets we could receive license fees and substantive milestone payments of more than $1.4 billion, including up to $358.5 million for the achievement of development milestones, up to $506.5 million for the achievement of regulatory milestones and up to $570 million for the achievement of commercialization milestones. The development milestones exclude the $5 million milestone payment we earned in October 2011. We will earn the next milestone payment of $2 million upon demonstrating in-vivo efficacy for the next drug discovery target. In addition, we will receive up to double-digit royalties on sales from any product that GSK successfully commercializes under this alliance.

During the three and nine months ended September 30, 2011, we recognized revenue of $2 million and $10.7 million, respectively, from our relationship with GSK which represented 10 percent and 16 percent, respectively, of our total revenue for those periods compared to $6.8 million and $8.5 million for the same periods in 2010. Our balance sheet at September 30, 2011 and December 31, 2010 included deferred revenue of $27.2 million and $29.8 million, respectively, related to the upfront and expansion payments.

Genzyme Corporation, a Sanofi company

In January 2008, we entered into a strategic alliance with Genzyme focused on the licensing and co-development of mipomersen and a research relationship. The license and co-development agreement provides Genzyme with exclusive worldwide rights for all therapeutic purposes to our patents and know-how related to mipomersen, including the key product related patents described in the “Patent and Proprietary Rights” section under “ApoB and Mipomersen” on page 28 of our Annual Report on Form 10-K for the year ended December 31, 2010, and their foreign equivalents pending world-wide in various countries, including in the European Union via the European Patent Convention, Japan, Canada, Australia, New Zealand and India. In addition, we agreed that we would not develop or commercialize another oligonucleotide-based compound designed to modulate apolipoprotein B-100 by binding to the mRNA encoding apolipoprotein B-100, throughout the world.

The transaction, which closed in June 2008, included a $175 million licensing fee, a $150 million equity investment in our stock in which we issued Genzyme five million shares of our common stock at $30 per share and a share of worldwide profits on mipomersen and follow-on drugs ranging from 30 percent to 50 percent of all commercial sales. We may also receive over $1.5 billion in substantive milestone payments upon the achievement of pre-specified events, including up to $750 million for the achievement of regulatory milestones and up to $825 million for the achievement of commercialization milestones. The next milestone payment we could potentially earn under our agreement with Genzyme is $25 million when the FDA accepts the NDA for mipomersen.

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Under this alliance, Genzyme is responsible for the continued development and commercialization of mipomersen. We agreed to supply the active pharmaceutical ingredient for mipomersen for the Phase 3 clinical trials and initial commercial launch. Genzyme is responsible for manufacturing the finished drug product for mipomersen, including the initial commercial launch supply, and, if approved, Genzyme will be responsible for the long term supply of mipomersen drug substance and finished drug product. In addition, we will contribute up to the first $125 million in funding for the development costs of mipomersen, which we expect to meet in 2011. Thereafter, we and Genzyme will share external development costs equally. Our initial development funding commitment and the shared funding will end when the program is profitable. As part of our alliance, Genzyme has a first right of negotiation for ISIS-SOD1$_{Rx}$.

The license and co-development agreement for mipomersen will continue in perpetuity unless earlier terminated by us or Genzyme under the following situations:

- Genzyme may terminate the license and co-development agreement at any time by providing written notice to Isis;
- We may terminate the license and co-development agreement on a country-by-country basis or in its entirety upon Genzyme's uncured failure to use commercially reasonable efforts to develop and commercialize mipomersen in the United States, France, Germany, Italy, Spain, the United Kingdom, Japan and Canada; and
- Either we or Genzyme may terminate the license and co-development agreement upon the other party's uncured failure to perform a material obligation under the agreement.

Upon termination of the license and co-development agreement, the license we granted to Genzyme for mipomersen will terminate and Genzyme will stop selling the product. In addition, if Genzyme voluntarily terminates the agreement or we terminate the agreement in a country or countries for Genzyme's failure to develop and commercialize mipomersen, then the rights to mipomersen will revert back to us and we may develop and commercialize mipomersen in the countries that are the subject of the termination, subject to a royalty payable to Genzyme.

If we are the subject of an acquisition, then within 180 days following the acquisition, Genzyme may elect to purchase all of our rights to receive payments under the mipomersen license and co-development agreement for a purchase price to be mutually agreed to by us and Genzyme, or, if we cannot agree, a fair market value price determined by an independent investment banking firm.

Genzyme has agreed that it will not sell the Isis stock that it purchased in February 2008 until the earlier of four years from the date of our mipomersen license and co-development agreement, the first commercial sale of mipomersen or the termination of our mipomersen license and co-development 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 and co-development agreement or the date Genzyme holds less than two percent 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. We are amortizing this $100 million 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 current research and development plan. During the three and nine months ended September 30, 2011, we recognized revenue of $16.6 million and $49.9 million, respectively, primarily related to the upfront payments we received from Genzyme, which represented 80 percent and 75 percent, respectively, of our total revenue for those periods compared to $16.8 million and $50.2 million for the same periods in 2010. Our balance sheets at September 30, 2011 and December 31, 2010 included deferred revenue of $44.3 million and $94.1 million, respectively.

Ortho-McNeil-Janssen Pharmaceuticals, Inc., formerly Ortho-McNeil, Inc.

In September 2007, we entered into a collaboration with OMJP to discover, develop and commercialize antisense drugs to treat metabolic diseases, including type 2 diabetes. As part of the collaboration, we granted OMJP worldwide development and commercialization rights to two of our diabetes programs, our glucagon receptor, or GCGR, and glucocorticoid receptor, or GCCR, programs. The collaboration ended and we regained the rights to drugs from both of these programs. We intend to move forward a more potent inhibitor for our GCGR program, which we identified as part of our collaboration with OMJP. We also intend to move forward the GCCR program. During the three and nine months ended September 30, 2011 and 2010, we did not recognize any revenue from our relationship with OMJP.

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Bristol-Myers Squibb

In May 2007, we entered into a collaboration agreement with Bristol-Myers Squibb to discover, develop and commercialize novel antisense drugs targeting proprotein convertase subtilisin/kexin type 9, or PCSK9. Under the terms of the agreement, we received a $15 million upfront licensing fee and Bristol-Myers Squibb agreed to provide us with at least $9 million in research funding over an initial period of three years. We finished amortizing the $15 million upfront fee into revenue when our period of performance under the original agreement ended in April 2010.

In April 2008, Bristol-Myers Squibb designated the first development candidate resulting from the collaboration for which we earned a $2 million milestone payment. In March 2010, we earned a $6 million milestone payment from the initiation of clinical studies. In 2010, Bristol-Myers Squibb stopped the Phase 1 study of the first development candidate and discontinued development of the drug. In July 2010, we and Bristol-Myers Squibb extended our collaboration and license agreement by two years to work together to discover a more potent PCSK9 antisense drug to move into development.

Under the agreement, we may receive up to $245 million for the achievement of substantive pre-specified development and regulatory milestones, including up to $50 million for the achievement of development milestones and up to $195 million for the achievement of regulatory milestones. We will earn the next milestone payment of $2 million if Bristol-Myers Squibb selects a more potent PCSK9 antisense drug development candidate. Bristol-Myers Squibb will also pay us royalties on sales of products resulting from the collaboration.

During the three and nine months ended September 30, 2011, we recognized revenue of $575,000 and $2 million, respectively, related to the upfront licensing fee, milestone payments and the research funding from Bristol-Myers Squibb compared to $700,000 and $11.4 million for the same periods in 2010. Revenue for the three and nine months ended September 30, 2011 represented three percent of our total revenue for each of those periods.

Eli Lilly and Company

In August 2001, we formed a broad strategic relationship with Eli Lilly and Company, which included a joint research collaboration. As part of the collaboration, Eli Lilly and Company licensed LY2181308, an antisense inhibitor of survivin, and LY2275796, an antisense inhibitor of eIF-4E, or eukaryotic initiation factor-4E. Eli Lilly and Company is responsible for the preclinical and clinical development of LY2181308.

As of September 30, 2011, we had earned $4.1 million in license fees and milestone payments related to the continued development of LY2181308. We may receive additional substantive milestone payments aggregating up to $25 million, including up to $5 million for the achievement of development

milestones, up to $8 million for the achievement of regulatory milestones and up to $12 million for the achievement of commercialization milestones and royalties. We will earn the next milestone of $5 million if Eli Lilly and Company initiates a Phase 3 study of LY2181308.

In December 2009, we reacquired LY2275796, renamed ISIS-EIF4E$_{Rx}$, and we are continuing to develop the drug. Eli Lilly and Company has the right to reacquire ISIS-EIF4E$_{Rx}$ on predefined terms prior to the initiation of Phase 3 development. However, if we publicly disclose the results from a Phase 2 clinical study of ISIS-EIF4E$_{Rx}$:

- Eli Lilly and Company may license ISIS-EIF4E$_{Rx}$ on the predefined terms;
- Eli Lilly and Company may tell us it is not interested in licensing ISIS-EIF4E$_{Rx}$, in which case we may license ISIS-EIF4E$_{Rx}$ to another partner; or
- Eli Lilly and Company may offer to license ISIS-EIF4E$_{Rx}$ on terms that are lower than the predefined terms, in which case we may license ISIS-EIF4E$_{Rx}$ to another partner so long as the licensing terms we reach with the new partner are better than terms offered by Eli Lilly and Company and we have not publicly disclosed any results from a new clinical study of ISIS-EIF4E$_{Rx}$ prior to reaching the agreement with the new partner.

During the three and nine months ended September 30, 2011 and 2010, we did not recognize any revenue from our relationship with Eli Lilly and Company.

Drug Discovery and Development Satellite Company Collaborations

Altair Therapeutics Inc.

In October 2007, we licensed AIR645 to Altair, a biotechnology company that was focused on the discovery, development and commercialization of novel therapeutics to treat human respiratory diseases. We granted an exclusive worldwide license to Altair for the development and commercialization of AIR645, an antisense drug for the treatment of asthma. Altair evaluated AIR645 in patients with asthma in a Phase 2 study. In this study, treatment with AIR645 reduced its intended target and patients tolerated the drug well. However, reducing the target did not produce enough therapeutic benefit to warrant continued development and Altair discontinued the program. In December 2010, we and Altair terminated our collaboration and license agreement and we reacquired AIR645 as well as Altair's assets related to AIR645. Altair distributed cash to its preferred shareholders in December 2010, and we received $408,000 from that distribution. Our ownership of Altair was less than 10 percent at September 30, 2011 and December 31, 2010.

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During the three and nine months ended September 30, 2011, we did not recognize any revenue from our relationship with Altair. Also, during the three months ended September 30, 2010 we did not recognize any revenue from our relationship with Altair compared to $17,000 for the nine months ended September 30, 2010.

Antisense Therapeutics Limited

In December 2001, we licensed ATL1102 to ATL, an Australian company publicly traded on the Australian Stock Exchange and in February 2008, ATL licensed ATL1102 to Teva Pharmaceutical Industries Ltd. When Teva decided to continue the development of ATL1102, we earned $1.4 million of sublicense revenue, which we included in revenue in 2008. In 2009, we earned $2 million from Teva for manufacturing ATL1102 drug product. In March 2010, Teva terminated the licensing agreement for ATL1102 and returned to ATL rights to ATL1102.

In addition to ATL1102, ATL is currently developing ATL1103 for growth and sight disorders. ATL1103 is a product of our joint antisense drug discovery and development collaboration. In December 2010, ATL completed a successful offering and raised approximately $2.4 million that it will use to advance ATL1103. ATL pays us for access to our antisense expertise and for research and manufacturing services we may provide to ATL. In October 2009 we agreed to manufacture ATL1103 drug product for ATL in return for 18.5 million shares of ATL's common stock. Additionally, ATL will pay royalties to us on sales of ATL1102 and ATL1103. We may also receive a portion of the fees ATL receives if it licenses ATL1102 or ATL1103.

At September 30, 2011 and December 31, 2010, we owned less than 10 percent of ATL's equity. During the nine months ended September 30, 2011, we recognized revenue of $210,000. For the three months ended September 30, 2011, and for the three and nine months ended September 30, 2010, we did not recognize any revenue related to this collaboration. Our balance sheet at December 31, 2010 included deferred revenue of $210,000 related to our agreements with ATL.

Atlantic Pharmaceuticals Limited, formerly Atlantic Healthcare (UK) Limited

In March 2007, we licensed alicaforsen to Atlantic Pharmaceuticals, a UK-based specialty pharmaceutical company founded in 2006, which is developing alicaforsen for the treatment of ulcerative colitis, or UC, and other inflammatory diseases. Atlantic Pharmaceuticals is initially developing alicaforsen for pouchitis, a UC indication, followed by UC and other inflammatory diseases. In exchange for the exclusive, worldwide license to alicaforsen, we received a $2 million upfront payment from Atlantic Pharmaceuticals in the form of equity. In September 2010, we participated in Atlantic Pharmaceuticals' financing by agreeing to sell to Atlantic Pharmaceuticals alicaforsen drug substance in return for shares of Atlantic Pharmaceuticals' common stock. At September 30, 2011 and December 31, 2010, we owned approximately 12 percent of Atlantic Pharmaceuticals' equity.

Under the agreement, we could receive substantive milestone payments totaling up to $1.4 million for the achievement of regulatory milestones for multiple indications. Assuming Atlantic Pharmaceuticals successfully develops and commercializes alicaforsen, we will earn the next milestone payment of $600,000 if Atlantic Pharmaceuticals submits a New Drug Application for alicaforsen with the FDA. We will also receive royalties on future product sales of alicaforsen. Atlantic Pharmaceuticals is solely responsible for the continued development of alicaforsen. In 2010, Atlantic Pharmaceuticals announced that in response to requests received from healthcare professionals, it was to supply alicaforsen under international Named Patient Supply regulations for patients with inflammatory bowel disease, or IBD. Atlantic Pharmaceuticals is currently pursuing opportunities to fund further development of alicaforsen.

During the three and nine months ended September 30, 2011 and 2010, we did not recognize any revenue from our relationship with Atlantic Pharmaceuticals.

Excaliard Pharmaceuticals, Inc.

In November 2007, we entered into a collaboration with Excaliard to discover and develop antisense drugs for the local treatment of fibrotic diseases, including scarring. We granted Excaliard an exclusive worldwide license for the development and commercialization of certain antisense drugs. Excaliard made an upfront payment to us in the form of equity and paid us $1 million in cash for the licensing of an antisense oligonucleotide drug targeting expression of connective tissue growth factor, or CTGF, that is activated during skin scarring following the wound healing process. At September 30, 2011 and December 31, 2010, we owned less than 10 percent of Excaliard's equity and we have no remaining performance obligations.

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In 2010 and 2011, we participated in Excaliard's financings at nominal amounts to maintain our ownership percentage. In addition, assuming Excaliard successfully develops and commercializes drugs it licenses from us, we may receive substantive milestone payments totaling up to $47.7 million for the achievement of key clinical and regulatory milestones, including up to $7.7 million for the achievement of development milestones and up to $40.0 million for the achievement of regulatory milestones. We will earn the next milestone payment of $1.2 million if Excaliard initiates a Phase 3 study for EXC001. We will also receive royalties on antisense drugs that Excaliard develops and commercializes. We may also receive a portion of the fees Excaliard receives if it licenses drugs from our collaboration.

During the three and nine months ended September 30, 2011, we did not recognize any revenue from our relationship with Excaliard. Also, during the three months ended September 30, 2010 we did not recognize any revenue from our relationship with Excaliard compared to $3,000 for the nine months ended September 30, 2010.

iCo Therapeutics Inc.

In August 2005, we granted a license to iCo for the development and commercialization of iCo-007. iCo is developing iCo-007 for the treatment of various eye diseases caused by the formation and leakage of new blood vessels such as diabetic macular edema and diabetic retinopathy. iCo paid us a $500,000 upfront fee and may pay us substantive milestone payments totaling up to $48.4 million for the achievement of clinical and regulatory milestones for multiple indications, including up to $7.9 million for the achievement of development milestones and up to $40.5 million for the achievement of regulatory milestones. We will receive the next milestone payment of $4 million if iCo initiates a Phase 3 study for iCo-007. In addition, we will receive royalties on any product sales of this drug. Under the terms of the agreement, iCo is solely responsible for the clinical development and commercialization of the drug. In September 2007, iCo initiated Phase 1 clinical trials for iCo-007 and we earned a milestone payment of $1.25 million in the form of 936,875 shares of iCo's common stock.

Over the course of our relationship, iCo has paid us in a combination of cash and equity instruments, which included common stock and convertible notes. In February 2009, iCo completed a CAD $1.3 million financing to fund the completion of its Phase 1 clinical study of iCo-007. We participated in the financing at a nominal amount to maintain our ownership percentage. In January 2010, we exercised the warrants we held to purchase 1.1 million shares of iCo's common stock and as a result our ownership in iCo at September 30, 2011 and December 31, 2010 was approximately 12 percent.

During the three and nine months ended September 30, 2010, we did not recognize any revenue from our relationship with iCo. Also, during the three months ended September 30, 2011 we did not recognize any revenue from our relationship with iCo compared to $7,000 for the nine months ended September 30, 2011.

OncoGenex Technologies Inc., a subsidiary of OncoGenex Pharmaceuticals 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 and OncoGenex amended the co-development agreement pursuant to which OncoGenex became solely responsible for the costs, development and commercialization of OGX-011. In exchange, OncoGenex agreed to pay us royalties on sales of OGX-011 and to share consideration it receives from licensing OGX-011 to a third party, except for consideration received by OncoGenex for the fair market value of equity and reimbursement of research and development expenses.

Under the amended agreement, we assigned to OncoGenex our rights in the patents claiming the composition and therapeutic methods of using OGX-011, and granted OncoGenex a worldwide, nonexclusive license to our know-how and patents covering our core antisense technology and manufacturing technology solely for use with OGX-011. The key product related patent that we assigned to OncoGenex was U.S. Patent number 6,900,187 having an expiration date of at least 2020; and the key core antisense technology patents we licensed OncoGenex are U.S. Patent number 7,919,472 having an expiration date of 2026 and its foreign equivalents pending in Australia, Canada, the European Patent Convention and Japan. In addition, we agreed that so long as OncoGenex or its commercialization partner is using commercially reasonable efforts to develop and commercialize OGX-011, we will not research, develop or commercialize an antisense compound designed to modulate clusterin. The amended agreement will continue until OncoGenex or its commercialization partner is no longer developing or commercializing OGX-011 or until we terminate the agreement for an uncured failure by OncoGenex to make a payment required under the agreement.

In December 2009, OncoGenex granted Teva the exclusive worldwide right and license to develop and commercialize any products containing OGX-011 and related compounds, with OncoGenex having an option to co-promote OGX-011 in the United States and Canada, for which we received $10 million of the upfront payment OncoGenex received from Teva. We are also eligible to receive 30 percent of up to $370 million in milestone payments OncoGenex may receive from Teva in addition to royalties on sales of OGX-011 ranging between 3.88 percent and seven percent. Under the agreement, this royalty is due on a country by country basis until the later of ten years following the first commercial sale of OGX-011 in the relevant country, and the expiration of the last patent we assigned or licensed to OncoGenex that covers the making, using or selling of OGX-011 in such country.

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To facilitate the execution and performance of OncoGenex's agreement with Teva, we and OncoGenex amended our license agreement primarily to give Teva the ability to cure any future potential breach by OncoGenex under our agreement. As part of this amendment, OncoGenex agreed that if OncoGenex is the subject of a change of control with a third party, where the surviving entity immediately following such change of control has the right to develop and sell OGX-011, then a payment of $20 million will be due and payable to Isis 21 days following the first commercial sale of the product in the United States. Any non-royalty payments OncoGenex previously paid to us are creditable towards the $20 million payment, so as a result of the $10 million payment we received from OncoGenex related to its license to Teva, the remaining amount owing in the event of a change of control as discussed above is a maximum of $10 million.

In August 2003, we and OncoGenex entered into a separate collaboration and license agreement for the development of a second-generation antisense anti-cancer drug, OGX-225. OncoGenex is responsible for all development costs and activities, and we have no further 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, including up to $1.5 million for the achievement of development milestones and up to $2 million for the achievement of regulatory milestones. In addition, we will receive royalties on future product sales of the drug. As of September 30, 2011, OncoGenex had not achieved any milestone events related to OGX-225. We will earn the next milestone payment of $500,000 if OncoGenex initiates a Phase 2 study for OGX-225.

In January 2005, we entered into a further agreement with OncoGenex to allow for the development of an additional second-generation antisense anti-cancer drug. Under the terms of the agreement, OncoGenex is responsible for all development costs and activities, and we have no further performance obligations. In April 2005, OncoGenex selected OGX-427 to develop under the collaboration. OncoGenex will pay us substantive milestone payments totaling up to $5.8 million for the achievement of key clinical and regulatory milestones, including up to $1.3 million for the achievement of development milestones and up to $4.5 million for the achievement of regulatory milestones. We will also receive royalties on future product sales of the drug. In January 2011, we earned a $750,000 milestone payment related to OncoGenex's phase 2 trial in men with metastatic prostate cancer. We will earn the next milestone payment of $1.3 million if OncoGenex initiates a Phase 3 study for OGX-427.

During 2009, we sold all of the common stock of OncoGenex that we owned resulting in net cash proceeds of $2.8 million. As of December 31, 2009, we no longer owned any shares of OncoGenex. During the nine months ended September 30, 2011, we recognized $750,000 in revenue from our relationship with OncoGenex. For the three months ended September 30, 2011 and for the three and nine months ended September 30, 2010, we did not recognize any revenue from our relationship with OncoGenex. Our balance sheet at December 31, 2010 included deferred revenue of $750,000 related to our relationship with Oncogenex.

Xenon Pharmaceuticals Inc.

In November 2010, we established a collaboration with Xenon to discover and develop antisense drugs as novel treatments for the common disease anemia of inflammation, or AI. AI is the second most common form of anemia worldwide and is associated with a wide variety of conditions including infection, cancer and chronic inflammation. We received an upfront payment in the form of a convertible promissory note from Xenon to discover and develop antisense drugs to the targets hemojuvelin and hepcidin. In addition to license and option fees, we are eligible to receive development and commercial milestone payments and royalties on sales of drugs licensed to Xenon under the collaboration and a portion of sublicense revenue. If Xenon identifies a development candidate, Xenon may take an exclusive license for the development and worldwide commercialization for this development candidate.

Under our collaboration agreement with Xenon we may receive up to $300 million in substantive milestone payments for multiple indications upon the achievement of pre-specified events, including up to $30 million for the achievement of development milestones, up to $150 million for the achievement of regulatory milestones and up to $120 million for the achievement of commercialization milestones. We will earn the next milestone payment of $2 million if Xenon selects a development candidate.

During the three and nine months ended September 30, 2011 and 2010, we did not recognize any revenue from our relationship with Xenon.

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Technology Development Satellite Company Collaborations

Achaogen, Inc.

In 2006, we exclusively outlicensed to Achaogen, Inc. specific know-how, patents and patent applications relating to aminoglycosides. Aminoglycosides are a class of small molecule antibiotics that inhibit bacterial protein synthesis and that clinicians use to treat serious bacterial infections. In exchange, Achaogen agreed to certain payment obligations related to aminoglycosides developed by Achaogen. Achaogen is developing plazomicin (formerly ACHN-490), an aminoglycoside discovered by Achaogen based on the technology we licensed to Achaogen. Plazomicin has displayed broad-spectrum activity in animals against multi-drug resistant Gram-negative bacteria that cause systemic infections, including E. coli. The compound has also demonstrated activity against methicillin-resistant staphylococcus aureus, or MRSA.

In connection with the license, Achaogen issued to us $1.5 million of Achaogen Series A Preferred Stock. In January 2009, we received a $1 million payment from Achaogen, consisting of $500,000 in cash and $500,000 in Achaogen securities, as a result of the filing of an IND for Achaogen's aminoglycoside drug, ACHN-490. In 2010, we received a $2 million payment from Achaogen as a result of the initiation of a Phase 2 study of ACHN-490. At September 30, 2011 and December 31, 2010, we owned less than 10 percent of Achaogen's equity. In addition, assuming Achaogen successfully develops and commercializes the first two drugs, we may receive payments totaling up to $46.3 million for the achievement of key clinical, regulatory and sales events. We will also receive royalties on sales of drugs resulting from the program. Achaogen is solely responsible for the continued development of Plazomicin.

During the three and nine months ended September 30, 2010, we recognized $2 million in revenue from our relationship with Achaogen. We did not recognize any revenue from our relationship with Achaogen for the same periods in 2011.

Archemix Corp.

In August 2007, we and Archemix entered into a strategic alliance focused on aptamer drug discovery and development. Archemix obtained a license to our technology for aptamer drugs, which take advantage of the three-dimensional structure of oligonucleotides to bind to proteins rather than targeting messenger ribonucleic acid, or mRNA. Through this licensing partnership, we are providing access to our oligonucleotide chemistry and other relevant patents to facilitate the discovery and development of aptamer drugs based on Archemix's technology. In November 2007, we received a $250,000 payment from Archemix associated with the initiation of Phase 2a trials of their aptamer drug. In May 2009, we received a nominal payment from Archemix related to the advancement of their aptamer drug that incorporates our technology. We will receive a portion of any sublicensing fees Archemix generates as well as up to $1.5 million for the achievement of pre-specified events and royalties on Archemix' drugs that use our technology.

During the three and nine months ended September 30, 2011 and 2010, we did not recognize any revenue from our relationship with Archemix.

Alnylam Pharmaceuticals, Inc.

In March 2004, we entered into a strategic alliance with Alnylam to develop and commercialize RNA interference, or RNAi, therapeutics. Under the terms of the agreement, we exclusively licensed to Alnylam our patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a $5 million technology access fee, participation in fees for Alnylam's partnering programs, as well as future milestone and royalty payments from Alnylam. For each drug Alnylam develops under this alliance, we may receive up to $3.4 million in substantive milestone payments, including up to $1.1 million for the achievement of development milestones and $2.3 million for regulatory milestones. In December 2010, we earned a $375,000 milestone payment from Alnylam for the initiation of a Phase 1 study in their transthyretin, or TTR, program. We will earn the next milestone payment of $750,000 if Alnylam initiates a Phase 3 study for TTR. We retained rights to a limited number of double-stranded RNAi therapeutic targets and all rights to single-stranded RNAi, or ssRNAi, therapeutics. We also made a $10 million equity investment in Alnylam at the time of the agreement. During 2007, 2006 and 2005, we sold our holdings of Alnylam stock resulting in aggregate net cash proceeds of $12.2 million and a net gain on investments of $6.2 million. As of December 31, 2007, we no longer own any shares of Alnylam.

In turn, Alnylam nonexclusively licensed to us its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry to research, develop and commercialize ssRNAi therapeutics and to research double-stranded RNAi compounds. We also received a license to develop and commercialize double-stranded RNAi drugs targeting a limited number of therapeutic targets on a nonexclusive basis. If we develop or commercialize an RNAi-based drug using Alnylam's technology, we will pay Alnylam milestone payments and royalties. For each drug, the potential milestone payments to Alnylam total $3.4 million, which we will pay upon the occurrence of specified development and regulatory events. As of September 30, 2011, we did not have an RNAi-based drug in clinical development.

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In April 2009, we and Alnylam amended our strategic collaboration and license agreement to form a new collaboration focused on the development of single-stranded RNAi technology. Under the terms of the amended collaboration and license agreement, Alnylam paid us an upfront license fee of $11 million plus $2.6 million of research and development funding in 2009 and 2010. In November 2010, Alnylam terminated the ssRNAi research program and we recognized $4.9 million of revenue from the upfront fee that we were amortizing into revenue over the research term. As a result, any licenses to ssRNAi products granted by us to Alnylam under the agreement, and any obligation by Alnylam to pay milestone payments, royalties or sublicense payments to us for ssRNAi products under the agreement, terminated. We continue to advance the development of ssRNAi technology and during the course of the collaboration, we made improvements in the activity of ssRNAi compounds, including increased efficacy and potency as well as enhanced distribution.

As of September 30, 2011, we had earned a total of $37.1 million from Alnylam resulting from sublicenses of our technology for the development of RNAi therapeutics that Alnylam has granted to pharmaceutical partners. During the three and nine months ended September 30, 2010, we recognized $1.4 million and $4.1 million, in revenue from our relationship with Alnylam. During the three and nine months ended September 30, 2011, we did not recognize any revenue from our relationship with Alnylam.

AVI BioPharma, Inc., formerly Ercole Biotech, Inc.

In May 2003, we and Ercole entered an agreement in which each party cross-licensed its respective intellectual property related to alternative RNA splicing. As part of the agreement, we granted Ercole an additional license to some of our chemistry patents. Assuming Ercole successfully develops and commercializes a drug incorporating the splicing technology or chemistry we licensed to Ercole, we may receive payments totaling up to $21 million for the achievement of key events. We will also receive royalties on sales of these drugs. Ercole is solely responsible for the continued development of its drugs.

Similarly, if we successfully develop and commercialize a drug incorporating the splicing technology Ercole licensed to us, we will pay Ercole up to $21 million for the achievement of key clinical, regulatory and sales events and will also pay royalties to Ercole on sales of these drugs. We currently do not have a drug incorporating Ercole's technology in clinical development.

In March 2008, AVI BioPharma, Inc. acquired Ercole's rights and obligations under the collaboration agreement. As a result of our collaboration agreement with Ercole, as part of the acquisition, we received a warrant to purchase 238,228 shares of AVI's common stock at an exercise price of $0.1679 per share, and a warrant to purchase 207,757 shares of AVI's common stock at an exercise price of $3.61 per share. During the three and nine months ended September 30, 2011 and 2010, we did not recognize any revenue from our relationship with Ercole.

External Project Funding

CHDI Foundation, Inc.

In November 2007, we entered into an agreement with CHDI, which provided us funding for the discovery and development of an antisense drug for the treatment of Huntington's disease. In August 2011, we renewed our collaboration with CHDI. CHDI's funding builds upon an earlier successful collaboration between us and CHDI, in which CHDI funded proof-of-concept studies that demonstrated the feasibility of using antisense drugs to treat Huntington's disease. Under the terms of the new collaboration, we will receive funding from CHDI to identify and conduct IND-enabling studies on an antisense drug targeting the huntingtin gene. If we grant a license to a third party to commercialize our Huntington's disease program, we and CHDI will evenly split the proceeds from the license until CHDI has recouped its funding together with a return determined at a predefined interest rate. Thereafter, we will keep the full amount of any additional proceeds. In addition, CHDI will reimburse us for approximately $1.7 million of research-related expenses we incurred after the earlier collaboration ended in 2010, which we are amortizing over the initial period of our performance obligation.

During the three and nine months ended September 30, 2011, we recognized revenue of $997,000 from our relationship with CHDI compared to $206,000 for the nine months ended September 30, 2010. During the three ended September 30, 2010, we did not recognize any revenue from our relationship with CHDI. Our balance sheet at September 30, 2011 included deferred revenue of $203,000 related to our relationship with CHDI.

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ALS Association; The Ludwig Institute; Center for Neurological Studies; Muscular Dystrophy Association

In October 2005, we entered a collaboration agreement with the Ludwig Institute, the Center for Neurological Studies and researchers from these institutions to discover and develop antisense drugs in the areas of ALS, also known as Lou Gehrig's disease, and other neurodegenerative diseases. Under this agreement, we agreed to pay the Ludwig Institute and Center for Neurological Studies modest milestone payments and royalties on any antisense drugs resulting from the collaboration. The researchers from the Ludwig Institute and Center for Neurological Studies, through funding from the ALS Association and the Muscular Dystrophy Association, conducted IND-enabling preclinical studies of ISIS-SOD1$_{RX}$. The ALS Association and the Muscular Dystrophy Association provided funding to offset the costs of the Phase 1 study of ISIS-SOD1$_{RX}$. Except for the funding provided by the ALS Association and the Muscular Dystrophy Association, we control and are responsible for funding the continued development of ISIS-SOD1$_{RX}$.

Intellectual Property Sale and Licensing Agreements

Out-Licensing Arrangements; Royalty Sharing Agreements; Sales of IP

Abbott Molecular Inc.

In January 2009, we sold our former subsidiary, Ibis Biosciences, to Abbott Molecular Inc., or AMI, pursuant to a stock purchase agreement for a total acquisition price of $215 million plus the earn out payments described below.

Under the stock purchase agreement, AMI will pay us earn out payments equal to a percentage of Ibis' revenue related to sales of Ibis systems, including instruments, assay kits and successor products, from the date of the acquisition closing through December 31, 2025. The earn out payments will equal five percent of Ibis' cumulative net sales over $140 million and up to $2.1 billion, and three percent of Ibis' cumulative net sales over $2.1 billion. AMI may reduce these earn out payments from five percent to as low as 2.5 percent and from three percent to as low as 1.5 percent, respectively, upon the occurrence of certain events. During 2010 and 2011 we did not recognize any revenue from our relationship with AMI.

Eyetech Pharmaceuticals, Inc.

In December 2001, we licensed to Eyetech certain of our patents necessary for Eyetech to develop, make and commercialize Macugen, a non-antisense drug for use in the treatment of ophthalmic diseases, that Eyetech is developing and commercializing with Pfizer Inc. Eyetech paid us a $2 million upfront fee and agreed to pay us for the achievment of pre-specified events and royalty payments in exchange for non-exclusive, worldwide rights to the intellectual property licensed from us. During 2004, we earned $4 million in payments, and our license with Eyetech may also generate additional payments aggregating up to $2.8 million for the achievement of specified regulatory events with respect to the use of Macugen for each additional therapeutic indication. Prior to 2010, we had assigned our rights to receive royalties for Macugen to Drug Royalty Trust 3.

During the three and nine months ended September 30, 2011, we recognized revenue of $195,000 and $604,000, respectively, of revenue related to royalties for Macugen under our license to Eyetech, compared to $230,000 and $378,000 for the same periods in 2010.

Roche Molecular Systems

In October 2000, we licensed some of our novel chemistry patents to Roche Molecular Systems, a business unit of Roche Diagnostics, for use in the production of Roche Molecular Systems' diagnostic products. The royalty-bearing license grants Roche Molecular Systems non-exclusive worldwide access to some of our proprietary chemistries in exchange for initial and ongoing payments from Roche Molecular Systems to us. In April 2011, we expanded our relationship with Roche Diagnostics by granting Roche a non-exclusive license to additional technology for research and diagnostic uses. During the three and nine months ended September 30, 2011, we recognized revenue of $216,000 and $630,000, respectively, from our relationship with Roche Molecular Systems, compared to $477,000 and $1.4 million for the same periods in 2010. Our balance sheet at December 31, 2010 included deferred revenue of $150,000 related to our agreements with Roche Molecular Systems.

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In-Licensing Arrangements

Idera Pharmaceuticals, Inc., formerly Hybridon, Inc.

We have an agreement with Idera under which we acquired an exclusive license to all of Idera's antisense chemistry and delivery technology related to our second generation antisense drugs and to double-stranded siRNA therapeutics. Idera retained the right to practice its licensed antisense patent technologies and to sublicense their technologies to collaborators under certain circumstances. In addition, Idera received a non-exclusive license to our suite of ribonuclease H, or RNase H, patents. For the three and nine months ended September 30, 2011, we recognized $10,000 in revenue for each of those periods, from our relationship with Idera, compared to $10,000 and $20,000 for the same periods in 2010.

Integrated DNA Technologies, Inc.

In March 1999, we further solidified our intellectual property leadership position in antisense technology by licensing certain antisense patents from IDT, a leading supplier of antisense inhibitors for research. The patents we licensed from IDT are useful in functional genomics and in making our

second-generation chemistry. We expect these patents will expire in February 2013. Under the license, we paid IDT $4.9 million in license fees in 2001 and we will pay royalties on sales of any drugs utilizing the technology we licensed from IDT until the patents expire.

University of Massachusetts

We have a license agreement with the University of Massachusetts under which we acquired an exclusive license to the University of Massachusetts' patent rights related to ISIS-SMN$_{Rx}$. If we successfully develop and commercialize a drug incorporating the technology we licensed from the University of Massachusetts, we will pay milestone payments to the University of Massachusetts totaling up to $650,000 for the achievement of key clinical and regulatory milestones. In addition, we will pay the University of Massachusetts a portion of any sublicense revenue we receive from sublicensing its technology, and a royalty on sales of ISIS-SMN$_{Rx}$ in the United States if our product incorporates the technology we licensed from the University of Massachusetts.

Verva Pharmaceuticals Ltd.

We have a license agreement with Verva under which we acquired an exclusive license to Verva's antisense patent rights related to ISIS-FGFR4$_{Rx}$. If we successfully develop and commercialize a drug incorporating the technology Verva licensed to us, we will pay milestone payments to Verva totaling up to $6.1 million for the achievement of key patent, clinical, and regulatory milestones. If we convert our license from an exclusive license to a nonexclusive license we could significantly reduce the milestone payments due to Verva. In addition, we will also pay royalties to Verva on sales of ISIS-FGFR4$_{Rx}$ if our product incorporates the technology we licensed from Verva.

Cold Spring Harbor Laboratory

We have a collaboration and license agreement with the Cold Spring Harbor Laboratory under which we acquired an exclusive license to the Cold Spring Harbor Laboratory's patent rights related to ISIS-SMN$_{Rx}$. If we successfully develop and commercialize a drug incorporating the technology we licensed from the Cold Spring Harbor Laboratory, we will pay milestone payments to the Cold Spring Harbor Laboratory totaling up to $900,000 for the achievement of key clinical and regulatory milestones. In addition, we will pay the Cold Spring Harbor Laboratory a portion of any sublicense revenue we receive from sublicensing the Cold Spring Harbor Laboratory's technology, and a royalty on sales of ISIS-SMN$_{Rx}$ if our product incorporates the technology we licensed from the Cold Spring Harbor Laboratory.

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7. Concentration of Business Risk

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2011	2010	2011	2010
Partner A	80%	59%	75%	61%
Partner B	10%	24%	16%	10%
Partner C	3%	2%	3%	14%

Contract receivables from one significant partner comprised approximately 54 percent of our contract receivables at September 30, 2011. Contract receivables from two significant partners comprised approximately 30 percent and 15 percent of our contract receivables at December 31, 2010. Included in our contract receivables at September 30, 2011 and December 31, 2010 was $646,000 and $544,000, respectively, representing 35 percent and 44 percent, respectively, of our contract receivables, due from Regulus.

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," refers to Isis Pharmaceuticals, Inc. and its subsidiaries, including Regulus Therapeutics Inc., its jointly owned subsidiary.

Forward-Looking Statements

In addition to historical information contained in this Report on Form 10-Q, this Report includes forward-looking statements regarding our business, the therapeutic and commercial potential of our technologies and products in development, and the financial position of Isis Pharmaceuticals, Inc. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs, including the planned commercialization of mipomersen, is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning our programs are described in additional detail in our Annual Report on Form 10-K for the year ended December 31, 2010, which is on file with the U.S. Securities and Exchange Commission, and those identified within this Item in the section entitled "Risk Factors" beginning on page 36 of this Report.

Overview

We are the leading company in antisense technology, exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs. Antisense technology is a direct route from genomics to drugs. With our highly efficient and prolific drug discovery platform we can expand our drug pipeline and our partners' pipelines with antisense drugs that address significant unmet medical needs. Our business strategy is to do what we do best—to discover unique antisense drugs and develop these drugs to key clinical value inflection points. In this way, our organization remains small and focused. We discover and conduct early development of new drugs, outlicense our drugs to partners and build a broad base of license fees, milestone payments and royalty income. We maximize the value of the drugs we discover by putting them in the hands of quality partners with late-stage development,

commercialization and marketing expertise such as Bristol-Myers Squibb, Genzyme, GSK and Eli Lilly and Company. We benefit from the expertise our partners bring to our drugs. For instance, our partner, Genzyme, plans to commercialize our lead product, mipomersen, following regulatory approval, which is expected in 2012. We also work with a consortium of smaller companies that can exploit our technology outside our primary areas of focus using their expertise in specific disease areas. We call these smaller companies our satellite companies. In addition to our cutting edge antisense programs, we maintain technology leadership through collaborations with Alnylam and Regulus, a company we established and jointly own focused on microRNA therapeutics. We also exploit our inventions with other therapeutic opportunities such as through collaborations with Achaogen and others. Beyond human therapeutics, we benefit from the commercialization of products incorporating our technology by other companies that are better positioned to maximize the commercial potential of these inventions, such as when we sold our subsidiary, Ibis Biosciences, to Abbott Molecular Inc. All of these different types of relationships are part of our unique business model and create current and future shareholder value.

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We protect our proprietary RNA-based technologies and products through our substantial patent estate. As an innovator in RNA-based drug discovery and development, we design and execute our patent strategy to provide us with extensive protection for our drugs and our technology. With our ongoing research and development, our patent portfolio continues to grow. The patents not only protect our key assets—our technology and our drugs—they also form the basis for lucrative licensing and partnering arrangements. To date, we have generated over $403 million from our intellectual property sale and licensing program that helps support our internal drug discovery and development programs.

The clinical success of mipomersen, the lead drug in our cardiovascular franchise, is a clear example of the power of our RNA-based technology. We and Genzyme reported positive data from four Phase 3 studies demonstrating consistent and robust lowering of low-density lipoprotein cholesterol, or LDL-C, and other atherogenic lipids. Across these four studies, treatment with mipomersen reduced LDL-C in patients who have persistently high LDL-C levels despite being treated on maximally tolerated lipid-lowering therapy. Mipomersen also reduced many other atherogenic lipids, including triglycerides, lipoprotein a, or Lp(a), and non-high-density lipoprotein cholesterol, or non HDL-C, due to its unique mechanism of action. We believe the safety profile of mipomersen supports our initial market opportunity in patients who cannot currently reach their recommended LDL-C goal. The mipomersen data from all four of our Phase 3 studies support the profile of the drug as a novel treatment to reduce LDL-C in patients with very high cholesterol, at high cardiovascular risk and who cannot reduce their LDL-C sufficiently with currently available lipid-lowering therapies. Genzyme has submitted a marketing authorization application to the European Medicines Agency for mipomersen. Genzyme remains on track to submit the U.S. application for marketing approval in the fourth quarter of 2011 and is actively preparing to launch mipomersen next year in the U.S. and Europe. If the necessary approvals are granted, Genzyme will market mipomersen under the brand name Kynamro.

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

In addition to mipomersen, many of the other drugs in our pipeline are demonstrating encouraging therapeutic activity in a variety of diseases. Over the past couple of years, we and our partners have reported positive data from five Phase 2 studies and seven Phase 1 studies. For example, we reported data from a positive Phase 2 study from our protein tyrosine phosphatase 1B, or PTP-1B, drug showing consistent and statistically significant reductions in short and intermediate measures of glucose control, reductions in LDL-C and a tendency toward weight loss. We believe these characteristics create an encouraging profile for a new therapy to treat type 2 diabetics. Many of our partnered drugs are also showing encouraging activity in numerous diseases. Our partner Excaliard reported data from three Phase 2 studies showing that treatment with EXC 001, a locally administered antisense drug, significantly reduced scarring in patients. These data highlight the broad therapeutic activity of antisense drugs and the power of our antisense technology platform to generate drugs that address significant medical needs.

The clinical successes of the drugs in our pipeline continue to result in new partnering opportunities. Since 2007, our partnerships have generated an aggregate of more than $840 million in payments from licensing fees, equity purchase payments, milestone payments and research and development funding. In addition, for our currently partnered programs we have the potential to earn approximately $3.5 billion in future milestone payments. We also will share in the future commercial success of our inventions and drugs resulting from these partnerships through earn out, profit sharing, and/or royalty arrangements. Our strong financial position is a result of the persistent execution of our business strategy as well as our inventive and focused research and development capabilities.

Recent Events

Drug Development and Corporate Highlights

- Dr. John Kastelein presented data from the mipomersen open-label extension study at the European Society of Cardiology Congress 2011. These data, in patients who have been treated with mipomersen for greater than one year, demonstrated sustained reductions in all measured atherogenic lipids with a safety profile consistent with the Phase 3 studies.
- Genzyme reached an agreement with the FDA on the design of the FOCUS FH study via a Special Protocol Assessment (SPA).
- We initiated Phase 1 studies on ISIS-GCGR$_{Rx}$ and ISIS-GCCR$_{Rx}$.
- We added a new drug candidate, ISIS-AAT$_{Rx}$ to our pipeline in our GSK collaboration. We earned a $5 million milestone payment.

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- We and CHDI renewed our collaboration to discover and develop an antisense drug for the treatment of Huntington's Disease.
- We filed a patent infringement lawsuit against Santaris Pharma based upon Santaris' commercial activities providing antisense drugs and antisense drug discovery services to several pharmaceutical companies.

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 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. In the following paragraphs, we describe the specific risks associated with these critical accounting policies. For all of these policies, we caution that future events rarely develop exactly as one may expect, and that best estimates routinely require adjustment.

Historically, adjustments to our estimates have had a material impact to our actual results on only one occasion. When Alnylam terminated the ssRNAi research program in November 2010, we recognized as revenue $4.9 million, which was the remaining deferred revenue from the upfront fee that we were amortizing into revenue over the research term. 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:

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

Except as set forth below, there have been no material changes to our critical accounting policies and estimates from the information provided in Item 7, “Management’s Discussion and Analysis of Financial Condition and Results of Operations”, included in our Annual Report on Form 10-K for the year ended December 31, 2010.

Revenue Recognition

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

Research and Development Revenue Under Collaborative Agreements

On January 1, 2011, we adopted an accounting standard, which amended the criteria to identify separate units of accounting for revenue arrangements with multiple deliverables. The new guidance replaces the concept of allocating revenue among deliverables in a multiple-element revenue arrangement according to fair value with an allocation based on selling price. The new standard is applicable on a prospective basis to agreements we entered into or materially modified after January 1, 2011. The adoption of the standard did not impact our financial position or results of operations as of and for the nine month period ended September 30, 2011 as we did not enter into or materially modify any multiple-element arrangements during that period. However, the adoption of this standard may result in revenue recognition for future agreements that is different from our existing multiple-element arrangements.

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For agreements that we entered into or materially modified prior to the adoption of the revised multiple element guidance, we recognize revenue from each element of the arrangement as long as we can determine a standalone value for the delivered element and fair value for the undelivered elements, we have completed our obligation to deliver or perform on that element and we are reasonably assured of collecting the resulting receivable.

We often enter into collaborations with multiple deliverables under which we receive non-refundable upfront payments. For collaborations where we determine that there is a single unit of accounting, we recognize revenue related to upfront payments ratably over our estimated period of performance relating to the term of the contractual arrangements. Occasionally, we must estimate our period of performance when the agreements we entered into do not clearly define such information. The revenue we recognize could be materially different if different estimates prevail. We have made estimates of our continuing obligations on several agreements, including our collaborations with ATL, Bristol-Myers Squibb, Genzyme, Eli Lilly and Company, OncoGenex and Pfizer. Our collaborative agreements typically include a research and/or development project plan that includes the activities the agreement requires each party to perform during the collaboration and the party responsible for performing them. We estimate the period of time over which we will complete the activities for which we are responsible and use that period of time as our period of performance for purposes of revenue recognition and amortize revenue over such period. If our collaborators ask us to continue performing work in a collaboration beyond the initial period of performance, we extend our amortization period to correspond to the new extended period of performance. The revenue we recognize could be materially different if different estimates prevail. We have made estimates of our continuing obligations on several agreements. Adjustments to performance periods and related adjustments to revenue amortization periods have had a material impact on our revenue on only one occasion. When Alnylam Pharmaceuticals, Inc. terminated the companies’ single-stranded RNAi, or ssRNAi, research program in November 2010, we recognized as revenue $4.9 million, which was the remaining deferred revenue from the upfront fee that we were amortizing into revenue over the research term.

As part of our Genzyme strategic alliance, in February 2008 Genzyme made a $150 million equity investment in us by purchasing five million shares of our common stock at $30 per share. The price Genzyme paid for our common stock represented a significant premium over the fair value of our stock. We accounted for this premium as deferred revenue and are amortizing it along with the $175 million licensing fee that we received in June 2008 ratably into revenue until June 2012, which represents the end of our performance obligation based on the current research and development plan.

Our collaborations often include contractual milestones, which typically relate to the achievement of pre-specified development, regulatory and commercialization events. These three categories of milestone events reflect the three stages of the life-cycle of our drugs, which we describe in more detail in the following paragraph.

Prior to the first stage in the life-cycle of our drugs, we perform a significant amount of work using our proprietary antisense technology to design chemical compounds which interact with specific genes that are good targets for drug discovery. From these research efforts, we hope to identify a development candidate. The designation of a development candidate is the first stage in the life-cycle of our drugs. A development candidate is a chemical compound that has demonstrated the necessary safety and efficacy in preclinical animal studies to warrant further study in humans. During the first step of the development stage, we or our partners study our drugs in IND-enabling studies, which are animal studies intended to support an IND application and/or the foreign equivalent. An approved IND allows us or our partners to study our development candidate in humans. If the regulatory agency approves the IND, we or our partners initiate Phase 1 clinical trials in which we typically enroll a small number of healthy volunteers to ensure the development candidate is safe for use in patients. If we or our partners determine that a development candidate is safe based on the Phase 1 data, we or our partners initiate Phase 2 studies that are generally larger scale studies in patients with the primary intent of determining the efficacy of the development candidate. The final step in the development stage is Phase 3 studies to gather the necessary safety and efficacy data to request marketing approval from the FDA, and/or foreign equivalents. The Phase 3 studies typically involve large numbers of patients and can take up to several years to complete. If the data gathered during the trials demonstrates acceptable safety and efficacy results, we or our partner will submit an application to the FDA or its foreign equivalents for marketing approval. This stage of the drug's life-cycle is the regulatory stage. If a drug achieves marketing approval, it moves into the commercialization stage, during which our partner will market and sell the drug to patients. Although our partner will ultimately be responsible for marketing and selling the drug, our efforts to discover and develop a drug that is safe, effective and reliable contributes significantly to our partner's ability to successfully sell the drug. The FDA and its foreign equivalents have the authority to impose significant restrictions on an approved drug through the product label and on advertising, promotional and distribution activities. Therefore, our efforts designing and executing the necessary animal and human studies are critical to obtaining claims in the product label from the regulatory agencies that would allow our partner to successfully commercialize our drug. Further, the patent protection afforded our drugs as a result of our initial patent applications and related prosecution activities in the United States and foreign jurisdictions are critical to our partner's ability to sell our drugs without competition from generic drugs. The potential sales volume of an approved drug is dependent on several factors including the size of the patient population, market penetration of the drug, and the price charged for the drug.

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Generally, the milestone events contained in our partnership agreements coincide with the progression of our drugs from development, to regulatory approval and then to commercialization. The process of successfully discovering a new development candidate, having it approved and ultimately sold for a profit is highly uncertain. As such, the milestone payments we may earn from our partners involve a significant degree of risk to achieve. Therefore, as a drug progresses through the stages of its life-cycle, the value of the drug generally increases.

Development milestones in our partnerships may include the following types of events:

- Designation of a development candidate. Following the designation of a development candidate, generally, IND-enabling animal studies for a new development candidate take 12 to 18 months to complete;
- Initiation of a Phase 1 clinical trial. Generally, Phase 1 clinical trials take one to two years to complete;
- Initiation or completion of a Phase 2 clinical trial. Generally, Phase 2 clinical trials take one to three years to complete;
- Initiation or completion of a Phase 3 clinical trial. Generally, Phase 3 clinical trials take two to four years to complete.

Regulatory milestones in our partnerships may include the following types of events:

- Filing of regulatory applications for marketing approval such as a New Drug Application in the United States or Marketing Authorization Application in Europe. Generally, it takes six to twelve months to prepare and submit regulatory filings.
- Marketing approval in a major market, such as the United States, Europe or Japan. Generally it takes one to two years after an application is submitted to obtain approval from the applicable regulatory agency.

Commercialization milestones in our partnerships may include the following types of events:

- First commercial sale in a particular market, such as in the United States or Europe.
- Product sales in excess of a pre-specified threshold, such as annual sales exceeding $1 billion. The amount of time to achieve this type of milestone depends on several factors including but not limited to the dollar amount of the threshold, the pricing of the product and the pace at which customers begin using the product.

We assess whether a substantive milestone exists at the inception of our agreements. When a substantive milestone is achieved, we recognize revenue related to the milestone payment. For our existing licensing and collaboration agreements in which we are involved in the discovery and/or development of the related drug or provide the partner with ongoing access to new technologies we discover, we determined that all future development, regulatory and commercialization milestones are substantive. For example, for our strategic alliance with GSK we are using our antisense drug discovery platform to seek out and develop new drugs against targets for rare and serious diseases. Alternatively, we provide on-going access to our technology to Alnylam to develop and commercialize RNA interference, or RNAi, therapeutics. We consider milestones for both of these collaborations to be substantive. For those agreements that do not meet the following criteria, we do not consider the future milestones to be substantive. In evaluating if a milestone is substantive we consider whether:

- Substantive uncertainty exists as to the achievement of the milestone event at the inception of the arrangement;
- The achievement of the milestone involves substantive effort and can only be achieved based in whole or part on our performance or the occurrence of a specific outcome resulting from our performance;

- The amount of the milestone payment appears reasonable either in relation to the effort expended or to the enhancement of the value of the delivered items;
- There is no future performance required to earn the milestone; and
- The consideration is reasonable relative to all deliverables and payment terms in the arrangement.

If any of these conditions are not met, we will defer recognition of the milestone payment and recognize it as revenue over the estimated period of performance, if any. In May 2011, we initiated a Phase 1 clinical study on ISIS-TTR$_{Rx}$, the first drug selected as part of our collaboration with GSK and in January 2011 OncoGenex Pharmaceuticals Inc., initiated a Phase 2 trial of OGX-427 in men with metastatic prostate cancer. We considered the initiation of Phase 1 and Phase 2 clinical trials to be substantive milestones because the level of effort and inherent risk associated with successfully moving a drug into Phase 1 and Phase 2 clinical development is high. Therefore, we recognized the entire $5 million milestone payment from GSK in the second quarter of 2011 and the entire $750,000 milestone payment from OncoGenex in the first quarter of 2011. Further information about our collaborative arrangements can be found in Note 6, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Condensed Consolidated Financial Statements.

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Licensing and Royalty Revenue

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

Results of Operations

Revenue

Total revenue for the three and nine months ended September 30, 2011 was $20.7 million and $66.7 million, respectively, compared to $28.6 million and $82.1 million for the same periods in 2010. Our revenue fluctuates based on the nature and timing of payments under agreements with our partners, including license fees, milestone-related payments and other payments. For example, revenue in the first nine months of 2011 included more revenue from GSK compared to 2010 due to the timing of the amortization of the upfront fee from GSK, which began in the second quarter of 2010. This increase in revenue was offset by less revenue from Bristol-Myers Squibb and no revenue from Alnylam Pharmaceuticals compared to the same period in 2010 because the amortization of upfront fees ended in 2010.

As our drugs advance in development, we earn milestone payments, but the timing of these payments fluctuates. For instance, in the first nine months in 2010, we recognized as revenue $13 million for milestone payments compared to approximately $6 million in milestone payments in the first nine months of 2011. Since the end of the third quarter, we have earned an additional $5 million milestone payment from GSK for designating ISIS-AAT$_{Rx}$ as a development candidate. Because we achieved this milestone in October, we will recognize revenue from the milestone payment in the fourth quarter of 2011.

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for the three and nine months ended September 30, 2011 was $20.2 million and $64.5 million, respectively, compared to $27.8 million and $77.5 million for the same periods in 2010. Lower revenue in the first nine months of 2011 compared to 2010 was primarily due to the timing of milestone payments and the timing of amortization of upfront fees. For example, revenue in the first nine months of 2011 included more revenue from GSK compared to 2010 due to the timing of the amortization of the upfront fee from GSK, which began in the second quarter of 2010, offset by less revenue from Bristol-Myers Squibb and no revenue from Alnylam Pharmaceuticals compared to the same period in 2010. Additionally, we recognized as revenue $13 million for milestone payments in the first nine months of 2010 compared to approximately $6 million in milestone payments in the first nine months of 2011.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties for the three and nine months ended September 30, 2011 was $524,000 and $2.2 million, respectively, compared to $839,000 and $4.6 million for the same periods in 2010. Revenue for the first nine months of 2011 was lower because in the second quarter of 2010 we earned $1.9 million from Regulus related to its strategic alliance with Sanofi.

Operating Expenses

Operating expenses for the three and nine months ended September 30, 2011 were $43.0 million and $119.2 million, respectively, compared to $37.6 million and $114.6 million for the same periods in 2010. Our operating expenses in the first nine months of 2011 reflected moderately higher costs associated with our maturing pipeline of drugs as these drugs move forward to more advanced stages of development, including into larger, longer clinical studies. While our share of mipomersen development expenses will be shared equally with Genzyme in 2012, many of the drugs in our pipeline will enter later-stage clinical development. Therefore, we expect our operating expenses to be moderately higher next year. These increases were offset by lower costs associated with the completion of the mipomersen Phase 3 program that supports the initial regulatory filings and lower non-cash compensation expense related to stock options resulting from a decrease in the average price of Isis' stock in 2011.

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

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Research and Development Expenses

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

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2011	2010	2011	2010
Research and development expenses	$ 37,907	$ 32,240	$ 103,584	$ 97,915
Non-cash compensation expense related to stock options	2,017	2,476	6,594	7,912
Total research and development	$ 39,924	$ 34,716	$ 110,178	$ 105,827

For the three and nine months ended September 30, 2011, we incurred total research and development expenses of $37.9 million and $103.6 million, respectively, compared to $32.2 million and $97.9 million for the same periods in 2010. Our year-to-date research and development expenses reflected moderately higher costs associated with our maturing pipeline of drugs as these drugs move forward to more advanced stages of development, including into larger, longer clinical studies. While our share of mipomersen development expenses will be shared equally with Genzyme in 2012, many of the drugs in our pipeline will enter later-stage clinical development. Therefore, we expect our operating expenses to be moderately higher next year. All amounts discussed exclude non-cash compensation expense related to stock options.

Antisense Drug Discovery

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

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

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2011	2010	2011	2010
Antisense drug discovery	$ 7,662	$ 8,481	$ 22,863	$ 24,520
Non-cash compensation expense related to stock options	581	722	1,893	2,304
Total antisense drug discovery	$ 8,243	$ 9,203	$ 24,756	$ 26,824

Antisense drug discovery costs for the three and nine months ended September 30, 2011 were $7.7 million and $22.9 million, respectively, compared to $8.5 million and $24.5 million for the same periods in 2010, all amounts exclude non-cash compensation expense related to stock options. Expenses in the first nine months of 2011 were lower compared to 2010 primarily due to a decrease in costs related to ongoing research activities. We expect our 2011 antisense drug discovery costs to be comparable to 2010.

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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,	
	2011	2010	2011	2010
Mipomersen	$ 4,409	$ 4,992	$ 10,386	$ 20,851
Other antisense development projects	12,470	6,249	31,767	17,412
Development overhead costs	1,635	1,511	4,744	4,269
Non-cash compensation expense related to stock options	697	779	2,217	2,461
Total antisense drug development	$ 19,211	$ 13,531	$ 49,114	$ 44,993

Antisense drug development expenditures for the three and nine months ended September 30, 2011 were $18.5 million and $46.9 million, respectively, compared to $12.8 million and $42.5 million for the same periods in 2010, all amounts exclude non-cash compensation expense related to stock options. The higher expenses in the first nine months of 2011 were primarily due to moderately higher costs associated with our maturing pipeline of drugs as these drugs move forward to more advanced stages of development, including into larger, longer clinical studies. These increases were offset by lower costs associated with the completion of the mipomersen Phase 3 program that supports the initial regulatory filings. While our share of mipomersen development expenses will be shared equally with Genzyme in 2012, many of the drugs in our pipeline will enter later-stage clinical development. Therefore, we expect our drug development expenditures to be moderately higher next year.

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, 11 of our 25 drug candidates, which substantially reduces our development costs. As part of our collaboration with Genzyme, we are over time transitioning the development responsibility to Genzyme and Genzyme will be responsible for the commercialization of mipomersen. We are contributing up to the first $125 million in funding for the development costs of mipomersen. We anticipate that we will reach $125 million in spending in the fourth quarter of 2011 or early in the first quarter of 2012, 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.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2011	2010	2011	2010
Manufacturing and operations	$ 4,258	$ 4,661	$ 13,543	$ 13,432
Non-cash compensation expense related to stock options	226	353	837	1,156
Total manufacturing and operations	$ 4,484	$ 5,014	$ 14,380	$ 14,588

Manufacturing and operations expenses for the three and nine months ended September 30, 2011 were $4.3 million and $13.5 million, respectively, compared to $4.7 million and $13.4 million for the same periods in 2010, all amounts exclude non-cash compensation expense related to stock options. Manufacturing and operations expense was essentially flat in the first nine months of 2011 compared to 2010.

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,	
	2011	2010	2011	2010
Personnel costs	$ 2,175	$ 1,959	$ 6,357	5,905
Occupancy	2,921	1,769	6,569	4,782
Depreciation and amortization	1,372	1,872	4,666	4,616
Insurance	216	224	643	705
Other	788	522	2,046	1,422
Non-cash compensation expense related to stock options	513	622	1,646	1,992
Total R&D support costs	$ 7,985	$ 6,968	$ 21,927	$ 19,422

R&D support costs for the three and nine months ended September 30, 2011 were $7.5 million and $20.3 million, respectively, compared to $6.3 million and $17.4 million for the same periods in 2010, all amounts exclude non-cash compensation expense related to stock options. The increase in expenses in 2011 compared to 2010 primarily relates to one-time occupancy and relocation costs associated with the move to our new facility and a reduction in the costs we allocated to Regulus. When Regulus moved to a separate facility in the second half of 2010, we significantly reduced the costs for facilities and support we were charging them.

General and Administrative Expenses

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

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2011	2010	2011	2010
General and administrative expenses	$ 2,758	$ 2,372	$ 7,987	$ 7,189
Non-cash compensation expense related to stock options	347	483	1,002	1,535
Total general and administrative expenses	$ 3,105	$ 2,855	$ 8,989	$ 8,724

General and administrative expenses for the three and nine months ended September 30, 2011 were $2.8 million and $8.0 million, respectively, increased compared to $2.4 million and $7.2 million for the same periods in 2010. The increase in expenses in 2011 compared to 2010 primarily relates to one-time occupancy and relocation costs associated with the move to our new facility and a reduction in the costs we allocated to Regulus. When Regulus moved to a separate facility in the second half of 2010, we significantly reduced the costs for facilities and support we were charging them.

Equity in Net Loss of Regulus Therapeutics Inc.

Our equity in net loss of Regulus for the three and nine months ended September 30, 2011 was $386,000 million and $2.3 million, respectively, compared to $930,000 and $6.4 million for the same periods in 2010. The decrease in our equity in net loss of Regulus reflected the decrease in Regulus' net loss in the first nine months of 2011 compared to the same period in 2010 resulting from the additional revenue Regulus earned from its alliance with Sanofi.

Investment Income

Investment income for the three and nine months ended September 30, 2011 was $575,000 million and $1.9 million, respectively, compared to $776,000 and $2.6 million for the same periods in 2010. The decrease in investment income was primarily due to a lower average return on our investments resulting from a lower average cash balance and current market conditions.

Interest Expense

Interest expense for the three and nine months ended September 30, 2011 was $4.8 million and $11.6 million, respectively, compared to $3.3 million and $9.8 million for the same periods in 2010. In the third quarter of 2011, there was an increase in interest expense as a result of additional interest expense associated with the non-cash amortization of the long-term liability for our new facility. See Note 5, *New Facility*, in the notes to the Condensed Consolidated Financial Statements for additional information about the accounting treatment for our new facility.

Gain (Loss) on Investments, Net

Net gain (loss) on investments was a net gain of $18,000 for the three months ended September 30, 2011 and a net loss of $267,000 for the nine months ended September 30, 2011 compared to a net loss on investments of $15,000 and $1.2 million for the same periods in 2010. The net loss on investments for the first nine months of 2011 was primarily due to a $359,000 valuation allowance we recorded related to our investment in Excaliard offset by nominal gains on our available-for-sale securities. The net loss on investments for the first nine months of 2010 primarily consists of an $880,000 non-cash loss related to the other-than-temporary impairment of our equity investment in ATL and $349,000 of valuation allowances we recorded related to the investments we made in Excaliard and Achaogen. Because realization of our Excaliard and Achaogen investments is uncertain we recorded a full valuation allowance.

Net Loss and Net Loss per Share

Net loss for the three and nine months ended September 30, 2011 was $26.9 million and $64.8 million, respectively, compared to $12.5 million and $47.3 million for the same periods in 2010. Basic and diluted net loss per share for the three and nine months ended September 30, 2011 was $0.27 per share and $0.65 per share, respectively, compared to $0.13 per share and $0.48 per share for the same periods in 2010. Our net loss for the first nine months of 2011 increased compared to the same period in 2010 primarily due to an increase in our net operating loss, which is discussed above, offset in part by a decrease in our share of Regulus' net loss.

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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, 2011, we have earned approximately $993.9 million in revenue from contract research and development and the sale and licensing of our intellectual property. From the time we were founded through September 30, 2011, we have raised net proceeds of approximately $822.1 million from the sale of our equity securities and we have borrowed approximately $568.5 million under long-term debt arrangements to finance a portion of our operations.

As of September 30, 2011, we had cash, cash equivalents and short-term investments of $364.8 million and stockholders' equity of $186.8 million. In comparison, we had cash, cash equivalents and short-term investments of $472.4 million and stockholders' equity of $244.5 million at December 31, 2010. At September 30, 2011, we had consolidated working capital of $293.5 million, compared to $377.2 million at December 31, 2010. The decrease in cash and working capital primarily relates to cash used for our operations.

As of September 30, 2011, our debt and other obligations totaled $217.0 million, compared to $144.3 million at December 31, 2010. The increase was primarily related to a $58.8 million increase in other long-term liabilities we were required to record related to the lease of our new facility as described below, $6.3 million of non-cash amortization of the debt discount we recorded in the first nine months of 2011, which increased the carrying value of our

2 5/8 percent convertible notes, and an additional draw down of $1.6 million on our equipment financing arrangement offset by $4.3 million of principal payments we made in the first nine months of 2011 on our equipment financing arrangement.

The following table summarizes our contractual obligations as of September 30, 2011. The table provides a breakdown of when obligations become due. We provide a more detailed description of the major components of our debt in the paragraphs following the table:

	Payments Due by Period (in millions)				
Contractual Obligations (selected balances described below)	**Total**	**Less than 1 year**	**1-3 years**	**3-5 years**	**After 5 years**
2 5/8 percent Convertible Subordinated Notes (principal and interest payable)	$ 173.2	$ 4.3	$ 168.9	$ —	$ —
Equipment Financing Arrangements (principal and interest payable)	$ 7.0	$ 4.1	$ 2.9	$ —	$ —
Other Obligations (principal and interest payable)	$ 1.5	$ 0.1	$ 0.1	$ 0.1	$ 1.2
New Facility Rent Payments	$ 150.9	$ 4.4	$ 12.0	$ 12.8	$ 121.7
Capital Lease	$ 0.8	$ 0.2	$ 0.4	$ 0.2	$ —
Operating Leases	$ 29.8	$ 2.0	$ 2.8	$ 2.7	$ 22.3
Total	$ 363.2	$ 15.1	$ 187.1	$ 15.8	$ 145.2

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

In January 2007, we completed a $162.5 million convertible debt offering, which raised proceeds of approximately $157.1 million, net of $5.4 million in issuance costs. We included the issuance costs in our balance sheet and are amortizing these costs to interest expense over the life of the debt. The $162.5 million convertible subordinated notes mature in 2027 and bear interest at 2 5/8 percent, which is payable semi-annually. The 2 5/8 percent notes are convertible, at the option of the note holders, into approximately 11.1 million shares of our common stock at a conversion price of $14.63 per share. We can redeem these notes at a redemption price equal to 100.75 percent of the principal amount between February 15, 2012 and February 14, 2013; 100.375 percent of the principal amount between February 15, 2013 and February 14, 2014; and 100 percent of the principal amount thereafter. Holders of the 2 5/8 percent notes may also require us to repurchase the 2 5/8 percent notes on February 15, 2014, February 15, 2017 and February 15, 2022, and upon the occurrence of certain defined conditions, at 100 percent of the principal amount of the 2 5/8 percent notes being repurchased plus unpaid interest.

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In October 2008, we entered into a loan agreement related to an equipment financing and in September 2009, we amended the loan agreement to increase the aggregate maximum amount of principal we can draw under the agreement. Under the loan agreement, we can borrow up to $18.4 million in principal to finance the purchase of equipment until the end of the draw down period. Each draw down under the loan agreement has a term of three years, with principal and interest payable monthly. We calculate interest on amounts we borrow under the loan agreement based upon the three year interest rate swap at the time we make each draw down plus four percent. We are using the equipment purchased under the loan agreement as collateral. In June 2011, we drew down an additional $1.6 million in principal under the loan agreement. As of September 30, 2011, we had drawn down $18.3 million in principal under this loan agreement at a weighted average interest rate of 6.19 percent. The carrying balance under this loan agreement at September 30, 2011 and December 31, 2010 was $6.7 million and $9.4 million, respectively. We will continue to use equipment lease financing as long as the terms remain commercially attractive.

In March 2010, we entered into a new lease agreement with an affiliate of BioMed Realty, L.P. Under the lease, BioMed has constructed a new facility in Carlsbad, California. The lease has an initial term of 20 years with an option to extend the lease for up to four five-year periods. Our rent under the new lease is based on a percentage of the total construction costs spent by BioMed to acquire the land and build the new facility. We are responsible for the costs associated with maintaining the facility. The leases on our former primary research and development facilities expire at the end of 2011. Rather than invest in costly renovations to these facilities, we chose to consolidate the majority of our operations in a new leased facility that Biomed Realty Trust, Inc. constructed. To make our move, which was completed in August 2011, as efficient as possible, we requested access to the new facility prior to the completion of construction. To gain early access, in May 2011, we agreed to modify our lease with BioMed to accept additional responsibility. As a result, accounting rules required us to record the cost of the facility as a fixed asset with a corresponding liability. In the third quarter of 2011, we consolidated the majority of our operations into the new facility. Therefore, beginning in the third quarter, we began depreciating the building over its economic life and our rent payments, which begin on January 1, 2012, will decrease the liability over the term of the lease.

In addition to contractual obligations, we had outstanding purchase orders as of September 30, 2011 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, cash equivalents and short-term investments to finance our activities. However, we may also pursue other financing alternatives, like issuing additional shares of our common stock, issuing debt instruments, refinancing our existing debt, or securing lines of credit. Whether we use our existing capital resources or choose to obtain financing will depend on various factors, including the future success of our business, the prevailing interest rate environment and the condition of financial markets generally.

RISK FACTORS

Investing in our securities involves a high degree of risk. You should consider carefully the following information about the risks described below, together with the other information contained in this report and in our other public filings in evaluating our business. If any of the following risks actually occur, our business could be materially harmed, and our financial condition and results of operations could be materially and adversely affected. As a result, the trading price of our securities could decline, and you might lose all or part of your investment. We have marked with an asterisk those risk factors that reflect substantive changes from the risk factors included in our Annual Report on Form 10-K for the year ended December 31, 2010.

Risks Associated with our Drug Discovery and Development Business

If we or our partners fail to obtain regulatory approval for our drugs, including mipomersen, we cannot sell them.*

We cannot guarantee that any of our drugs, including mipomersen, will be safe and effective, or will be approved for commercialization. We and our partners must conduct time-consuming, extensive and costly clinical studies to show the safety and efficacy of each of our drugs, including mipomersen, before a drug can be approved for sale. We must conduct these studies in compliance with Food and Drug Administration, or FDA, regulations and with comparable regulations in other countries.

We and our partners may not obtain necessary regulatory approvals on a timely basis, if at all, for any of our drugs, including mipomersen. Even though we have completed the Phase 3 program to support our initial market for mipomersen, Genzyme has filed for marketing approval for mipomersen in Europe, and Genzyme plans to file for marketing approval in the United States in 2011, it is possible that regulatory agencies will not approve mipomersen for marketing. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of any of our drugs, including mipomersen, the agency will not approve the specific drug or will require additional studies, which can be time consuming and expensive and which will delay commercialization of the drug.

Failure to receive marketing approval for our drugs, including mipomersen, or delays in these approvals could prevent or delay commercial introduction of the drug, and, as a result, could negatively impact our ability to generate revenue from product sales.

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If the results of clinical testing indicate that any of our drugs, including mipomersen, 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 drugs are a relatively new approach to therapeutics. If we cannot demonstrate that our drugs, including mipomersen, are safe and effective 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. Similar results could occur with any additional clinical studies for mipomersen and in clinical studies for our other drugs. If any of our drugs in clinical studies, including mipomersen, does not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for the drug and our stock price could decline.

Even if our drugs are successful in preclinical and human clinical studies, the drugs may not be successful in late-stage clinical studies.

Successful results in preclinical or initial human clinical studies, including the Phase 3 results for mipomersen and the Phase 2 results for some of our other drugs in development, may not predict the results of subsequent clinical studies, including subsequent studies of mipomersen. There are a number of factors that could cause a clinical study to fail or be delayed, including:

- the clinical study 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 study due to adverse side effects of a drug on subjects in the trial;
- we may decide, or regulators may require us, to conduct additional preclinical testing or clinical studies;
- enrollment in our clinical studies may be slower than we anticipate;
- the cost of our clinical studies may be greater than we anticipate; and
- the supply or quality of our drugs or other materials necessary to conduct our clinical studies may be insufficient, inadequate or delayed.

Any failure or delay in our clinical studies, including any further studies under our development program for mipomersen, could reduce the commercial potential or viability of our drugs.

Even if approved, mipomersen and any of our other drugs may be subject to regulatory limitations.

Following approval of a drug, we and our partners must comply with comprehensive government regulations regarding how we manufacture, market and distribute drug products. Even if approved, we may not obtain the labeling claims necessary or desirable for successfully commercializing our drug products, including mipomersen. The FDA has the authority to impose significant restrictions on an approved drug product through the product label and on advertising, promotional and distribution activities. If approved, the FDA may condition approval on the performance of post-approval clinical studies or patient monitoring, which could be time consuming and expensive. If the results of such post-marketing studies are not satisfactory, the FDA may withdraw marketing authorization or may condition continued marketing on commitments from us or our partners that may be expensive and/or time consuming to fulfill. In addition, if we or others identify side effects after any of our drug products are on the market, or if manufacturing problems occur subsequent to regulatory approval, we may lose regulatory approval, or we may need to conduct additional clinical studies and/or change the labeling of our drug products including mipomersen.

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

If mipomersen or any of our other drugs is approved for marketing, our success will depend upon the medical community, patients and third-party payors accepting our drug as medically useful, cost-effective and safe. Even if the FDA or foreign regulatory agencies approve mipomersen or our other drugs for commercialization, doctors may not use our drugs to treat patients. For example, we currently have one commercially approved drug, Vitravene, a

treatment for CMV retinitis in AIDS patients, which our partner is no longer marketing due to a dramatic decline in the incidence of CMV retinitis in AIDS patients. We and our partners may not successfully commercialize additional drugs.

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Additionally, in many of the markets where we may sell our drugs in the future, if we cannot agree with the government regarding the price we can charge for our drugs, then we may not be able to sell our drugs in that market.

The degree of market acceptance for mipomersen, and any of our other drugs, depends upon a number of factors, including the:

- receipt and scope of regulatory approvals;
- establishment and demonstration in the medical and patient community of the efficacy and safety of our drugs and their potential advantages over competing products;
- cost and effectiveness of our drugs compared to other available therapies;
- 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/or use any drugs that we may develop. In addition, cost control initiatives by governments or third party payors could decrease the price that we receive for mipomersen or our other drugs or increase patient coinsurance to a level that makes mipomersen or our other drugs unaffordable.

We depend on our collaboration with Genzyme for the development and commercialization of mipomersen.

We have entered into a collaborative arrangement with Genzyme to develop and commercialize mipomersen.

We entered into this collaboration primarily to:

- fund some of our development activities for mipomersen;
- seek and obtain regulatory approvals for mipomersen; and
- successfully commercialize mipomersen.

In general, we cannot control the amount and timing of resources that Genzyme devotes to our collaboration. If Genzyme fails to further develop and commercialize mipomersen, or if Genzyme's efforts are not effective, our business may be negatively affected. We are relying on Genzyme to obtain marketing approvals for and successfully commercialize mipomersen. Our collaboration with Genzyme may not continue or result in the successful commercialization of mipomersen. Genzyme can terminate our collaboration at any time. If Genzyme stopped developing or commercializing mipomersen, we would have to seek additional sources for funding and may have to delay or reduce our development and commercialization programs for mipomersen. If Genzyme does not successfully commercialize mipomersen, we may receive limited or no revenues for mipomersen. In addition, Sanofi recently acquired Genzyme which could disrupt Genzyme or distract it from performing its obligations under our collaboration.

If Genzyme cannot manufacture finished drug product for mipomersen or the post-launch supply of the active drug substance for mipomersen, mipomersen may not achieve or maintain commercial success.

We believe that our manufacturing facility has sufficient capacity to supply the drug substance necessary for the initial commercial launch of mipomersen, if approved. However, we rely on Genzyme to manufacture the finished drug product for mipomersen, including the initial commercial launch supply. In addition, if approved, Genzyme will be responsible for the long term supply of both mipomersen drug substance and finished drug product. Genzyme may not be able to reliably manufacture mipomersen drug substance and drug product to support mipomersen's long term commercialization. If Genzyme cannot reliably manufacture mipomersen drug substance and drug product, mipomersen may not achieve or maintain commercial success, which will harm our ability to generate revenue.

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

To successfully commercialize any of our drugs, we or our partner would need 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 drug costs. We may not be able to manufacture our drugs 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 and similar regulations in foreign countries, which the applicable regulatory authorities enforce through facilities inspection programs. We and our contract manufacturers may not comply or

maintain compliance with Good Manufacturing Practices, or similar foreign regulations. Non-compliance could significantly delay or prevent our receipt of marketing approval for our drugs, including mipomersen, or result in enforcement action after approval that could limit the commercial success of our drugs, including mipomersen.

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

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

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

These competitive developments could make our drugs, including mipomersen, 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 treat the same diseases our own collaborative programs target. 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, including mipomersen.

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 studies 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. Marketing and sales capability is another factor relevant to the competitive position of our drugs, and we will rely on our partners to provide this capability.

Regarding mipomersen, some competitors are pursuing a development strategy that competes with our strategy for mipomersen. Other companies are currently developing products that could compete with mipomersen. For example, products such as microsomal triglyceride transfer protein inhibitors, or MTP inhibitors, and other lipid lowering drugs other companies are developing could potentially compete with mipomersen. For example, Aegerion is currently evaluating its MTP inhibitor in a Phase 3 study in homozygous FH patients. Our revenues and financial position will suffer if mipomersen receives regulatory approval, but cannot compete effectively in the marketplace.

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

Risks Associated with our Businesses as a Whole

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

Because drug discovery and development requires substantial lead-time and money prior to commercialization, our expenses have generally exceeded our revenue since we were founded in January 1989. As of September 30, 2011, we had an accumulated deficit of approximately $821.5 million and stockholders' equity of approximately $186.8 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from research grants and the sale or licensing of our patents, as well as interest income. We have had only one product, Vitravene, approved for commercial use, but our exclusive distribution partner for this product no longer markets this product. We may 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 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 drug 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 unpartnered drugs. However, we may not be able to negotiate favorable collaborative arrangements for these drug programs. If we cannot continue to secure additional collaborative partners, our revenues could decrease and the development of our drugs could suffer.

Our corporate partners are developing and/or funding many of the drugs in our development pipeline, including ATL, Atlantic Pharmaceuticals, Bristol-Myers Squibb, iCo, Eli Lilly and Company, Genzyme, GSK, OncoGenex, and Teva Pharmaceutical Industries Ltd. If any of these pharmaceutical companies stops developing and/or funding these drugs, our business could suffer and we may not have, or be willing to dedicate, the resources available to develop these drugs on our own.

Our collaborators can terminate their relationships with us under certain circumstances, many of which are outside of our control. In the past, based on the disappointing results of Phase 3 clinical studies, we had a partner discontinue its investment in one of our drugs.

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 drug development programs.

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

- conduct clinical studies;
- seek and obtain regulatory approvals; and
- manufacture, market and sell our drugs.

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

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

- pursue alternative technologies or develop alternative products that may be competitive with the drug that is part of the collaboration with us;

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- 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.

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, including mipomersen.

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 study, 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 our investors' expectations, including milestones for approval of mipomersen, the price of our securities would likely decrease.

For example, in April 2008 the FDA provided guidance regarding approval requirements for mipomersen. The FDA indicated that reduction of LDL-C is an acceptable surrogate endpoint for accelerated approval of mipomersen for use in patients with HoFH. The FDA required us to include data from two preclinical studies for carcinogenicity in the HoFH filing, which studies we have now completed. The FDA also indicated that for broader indications in high risk, high cholesterol patients the FDA would require an outcome study. This FDA guidance caused us to revise our development plans and timelines such that in July 2011 Genzyme filed for marketing approval in Europe for the treatment of patients with HoFH and patients with severe HeFH and will seek marketing approval for the treatment of patients with HoFH in the United States in 2011.

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

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

It is possible that in the future we may have to defend our intellectual property rights. In the event of an intellectual property dispute, we may need 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 September 2011 we filed a patent infringement lawsuit against Santaris Pharma A/S and Santaris Pharma A/S Corp. in the United States District Court of the Southern District of California. This lawsuit may be costly and may not be resolved in our favor.

If a third party claims that our drugs 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 patent applications held by others that relate to our business. This is especially true since patent applications in the United States are filed

confidentially for the first 18 months. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain unresolved.

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

Many of our drugs are undergoing clinical studies or are in the early stages of research and development. All of our drug programs will require significant additional research, development, preclinical and/or clinical testing, regulatory approval and/or commitment of significant additional resources prior to their commercialization. As of September 30, 2011, we had cash, cash equivalents and short-term investments equal to $364.8 million. If we do not meet our goals to commercialize mipomersen or our other drugs, 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:

- marketing approval and successful launch of mipomersen;

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- 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 studies;
- the time and costs involved in obtaining regulatory approvals;
- competing technological and market developments, including the introduction by others of new therapies that address our markets; and
- the profile and launch timing of our drugs.

If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available at all or on acceptable terms. If we raise additional funds by issuing equity securities, the shares of existing stockholders will be diluted and the 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 or drugs.

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 studies 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, 2011, the market price of our common stock ranged from $6.55 to $10.63 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical study 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.

We are exposed to potential product liability claims, and insurance against these claims may not be available to us at a reasonable rate in the future or at all.

Our business exposes us to potential product liability risks that are inherent in the testing, manufacturing, marketing and sale of therapeutic products. We have clinical study insurance coverage and commercial product liability insurance coverage. However, this insurance coverage may not be adequate to cover claims against us, or be available to us at an acceptable cost, if at all. Regardless of their merit or eventual outcome, products liability claims may result in decreased demand for our drug products, injury to our reputation, withdrawal of clinical study volunteers and loss of revenues. Thus, whether or not we are insured, a product liability claim or product recall may result in losses that could be material.

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

Our research, development and manufacturing activities involve the use of potentially harmful biological materials as well as materials, chemicals and various radioactive compounds that could be hazardous to human health and safety or the environment. These materials and various wastes resulting from

their use are stored at our facilities in Carlsbad, California pending ultimate use and disposal. We cannot completely eliminate the risk of contamination, which could cause:

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

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

We depend on Regulus for development of our microRNA technology.

Regulus is a jointly owned company that we and Alnylam established to focus on discovery, developing, and commercializing of microRNA therapeutics. We exclusively licensed to Regulus our intellectual property rights covering microRNA technology. Regulus operates as an independent company, governed by a board of directors. We and Alnylam can elect an equal number of directors to serve on the Regulus Board. Regulus researches and develops microRNA projects and programs pursuant to an operating plan that its board approves. However, Regulus and its employees are ultimately responsible for researching and developing our microRNA technology. If Regulus is not successful, the value of our microRNA technology would be harmed and we would lose part or all of our investment in Regulus.

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

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

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

Our certificate of incorporation provides for classified terms for the members of our board of directors. Our certificate also includes a provision that requires at least 66²¤₃ percent of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15 percent or more of our voting stock, except in cases where certain directors approve the transaction or certain minimum price criteria and other procedural requirements are met.

Our certificate of incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. In addition, only our board of directors, chairman of the board or chief executive officer can call special meetings of our stockholders. We have in the past, and may in the future, implement 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. Our stockholders' rights plan expired in December 2010. These provisions, as well as Delaware law and other of our agreements, may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over then current market prices, and may limit the ability of our stockholders to approve transactions that they think may be in their best interests. In addition, our board of directors has the authority to fix the rights and preferences of, and issue shares of preferred stock, which may have the effect of delaying or preventing a change in control of our company without action by our stockholders.

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

In addition, our collaboration agreement with Genzyme regarding mipomersen provides that if we are acquired, Genzyme may elect to purchase all of our rights to receive payments under the mipomersen collaboration agreement for a purchase price to be mutually agreed 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 have registered for resale our $2^{5}/_{8}$ percent convertible subordinated notes, including the approximately 11.1 million shares issuable upon conversion of the notes. The addition of any of these shares into the public market may have an adverse effect on the price of our securities.

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

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

The SEC and other regulators have continued to adopt new rules and regulations and make additional changes to existing regulations that require our compliance. On July 21, 2010, the Dodd-Frank Wall Street Reform and Protection Act, or the Dodd-Frank Act, was enacted. There are significant corporate governance and executive compensation-related provisions in the Dodd-Frank Act that require the SEC to adopt additional rules and regulations in these areas such as "say on pay" and proxy access. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which may lead to additional compliance costs and impact the manner in which we operate our business.

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

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

ITEM 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

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

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ITEM 4. CONTROLS AND PROCEDURES

As of the end of the period covered by this Quarterly Report on Form 10-Q, we carried out an evaluation, under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended. Based on this evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of September 30, 2011. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to September 30, 2011.

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

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

PART II — OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

In September 2011, we filed a patent infringement lawsuit against Santaris Pharma A/S and Santaris Pharma A/S Corp. in the United States District Court of the Southern District of California. Our infringement lawsuit alleges that Santaris' activities providing antisense drugs and antisense drug discovery services to several pharmaceutical companies infringes U.S. Patent No. 6,326,199, entitled "Gapped 2' Modified Oligonucleotides" and U.S. Patent No. 6,066,500, entitled "Antisense Modulation of Beta Catenin Expression." In the lawsuit we are seeking monetary damages and an injunction enjoining Santaris from conducting or participating in the infringing activities. Santaris has not yet filed an answer to our complaint.

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

Not applicable

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable

ITEM 4. (REMOVED AND RESERVED)

Not applicable

ITEM 5. OTHER INFORMATION

Not applicable

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ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.1	Research Agreement dated August 10, 2011 between the Registrant and CHDI Foundation, Inc. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
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.
101	The following financial statements from the Isis Pharmaceuticals, Inc. Quarterly Report on Form 10-Q for the quarter ended September 30, 2011, formatted in Extensive Business Reporting Language (XBRL): (i) condensed consolidated balance sheets, (ii) condensed consolidated statements of operations, (iii) condensed consolidated statements of cash flows, and (iv) notes to condensed consolidated financial statements (tagged as blocks of text).

Isis Pharmaceuticals, Inc.

(Registrant)

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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 7, 2011
/s/ B. Lynne Parshall B. Lynne Parshall, J.D.	Director, Chief Operating Officer, Chief Financial Officer and Secretary (Principal financial and accounting officer)	November 7, 2011

Exhibit 10.1

Execution Copy

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

RESEARCH AGREEMENT

THIS RESEARCH AGREEMENT (this "***Agreement***"), dated as of August 10, 2011 (the "***Effective Date***"), is entered into by and between **ISIS PHARMACEUTICALS, INC.**, a Delaware corporation ("***Isis***"), and **CHDI FOUNDATION, INC.**, a New Jersey corporation formerly known as CHDI, Inc. (the "***Foundation***"). Isis and the Foundation will hereinafter be referred to individually as a "***Party***" and collectively as the "***Parties***".

The Foundation's mission is to rapidly discover and develop drugs that delay or slow the progression of Huntington's disease.

Isis is an RNA-based drug discovery and development company.

The Parties are parties to that certain Research Agreement (as amended, the "***2007 Research Agreement***"), dated October 22, 2007 (the "***Original Effective Date***"), pursuant to which the Foundation and Isis entered into a collaboration to seek therapies for Huntington's disease.

Since April 2010, the Parties ceased collaborating with one another under the 2007 Research Agreement.

After the Parties ceased collaborating under the 2007 Research Agreement, Isis continued to work on therapies for Huntington's disease without funding from the Foundation.

The Parties now desire to enter into this new Agreement to resume collaborating on therapies for Huntington's disease.

In consideration of the mutual representations, warranties and covenants contained herein and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties agree as follows:

Definitions

1. **Definitions.** For the purposes of this Agreement, the following terms have the meanings set forth below:

(a) "***2007 Research Agreement Project***" means the "Project" as defined in the 2007 Research Agreement.

(b) "***2007 Research Agreement Project Compound***" means any MOE Gapmer that was identified by Isis in the course of Isis' conduct of the 2007 Research Agreement Project, including any Project Human Compound.

(c) "***2007 Research Agreement Project Intellectual Property***" means any Intellectual Property conceived, discovered, invented, made or first reduced to practice in the course of Isis' conduct of the 2007 Research Agreement Project other than any such Intellectual Property that constitutes Isis Background Intellectual Property or Foundation Background Intellectual Property.

(d) "***2007 Research Agreement Project Results***" means all data, formulae, methods, outcomes, protocols or other results produced in the course of Isis' conduct of the 2007 Research Agreement Project.

(e) "***Acquired Party***" means the Party that consummates a Change of Control with an Acquirer.

(f) "***Acquirer***" means, with respect to a Party, the Third Party or Affiliate of such Party that is a party to a Change of Control with such Party after the Effective Date.

(g) **"*Acquirer Intellectual Property***" means, with respect to an Acquirer, (i) all Intellectual Property (A) owned by, or licensed by a Third Party to, such Acquirer immediately prior to the consummation of the Change of Control involving such Acquirer and a Party or (B) acquired by, or licensed to, such Acquirer from a Third Party after the consummation of the Change of Control involving such Acquirer and a Party and (ii) all Intellectual Property conceived, discovered, invented, made or first reduced to practice by the Acquirer (or on behalf of Acquirer by a Third Party) after the consummation of the Change of Control involving such Acquirer and a Party, other than in the course of the performance of the Research or using or practicing Project Intellectual Property. Notwithstanding the foregoing, Acquirer Intellectual Property shall not include a) any Intellectual Property that constitutes the Background Intellectual Property of the Acquired Party before or on the date of the consummation of the Change of Control involving such Acquirer and a Party or b) any Intellectual Property that constitutes Project Intellectual Property before, on or after the date of the consummation of the Change of Control involving such Acquirer and a Party.

(h) "***Additional Project Activities Description***" means the written document attached to this Agreement as Appendix C.

(i) "***Approved Foundation Requested Project Compound***" means a Foundation Requested Project Compound (as defined in Section 8(c)(i) of this Agreement) approved in accordance with Section 8(c)(ii) and Section 5 of this Agreement for use by the Foundation and/or a Foundation Collaborator in an Approved Foundation Project Compound Study.

(j) "***Approved Foundation Project Compound Study***" means a Foundation Project Compound Study (as defined in with Section 8(c)(i) of this Agreement) approved in accordance with Section 8(c)(ii) and Section 5 of this Agreement to be conducted by the Foundation and/or a Foundation Collaborator.

(k) "***ASO***" means an oligonucleotide compound, or analog thereof, having a sequence that is at least 6 bases long and that modulates expression of a gene target via the binding of such compound to a mRNA or pre-mRNA of such gene target.

(l) "***Affiliate***" means any Person which directly or indirectly controls, is controlled by or is under common control with another Person. As used in this definition, the term "control" means, as to any Person: (i) direct or indirect ownership of 80% or more of the voting interests or other ownership interests in a Person; or (ii) direct or indirect ownership of 80% or more of the interest in the income of the Person in question. A Person will cease to be an Affiliate of another Person if such control relationship no longer exists.

(m) "***Background Intellectual Property***" means Isis Background Intellectual Property and the Foundation Background Intellectual Property.

(n) "***Bankruptcy Event***" means the (i) making of a general assignment for the benefit of creditors by an entity; (ii) filing of any petition by an entity, or the commencement of any proceeding voluntarily by an entity, for any relief under any bankruptcy or insolvency laws or any law relating to the relief of debtors; (iii) consent by an entity to the entry of an order in an involuntary bankruptcy or insolvency case; (iv) entry of an order or decree for relief against an entity by a court of competent jurisdiction in an involuntary case under any bankruptcy or insolvency laws or any law relating to the relief of debtors, which order or decree is unstayed and in effect for a period of 90 consecutive days; (v) appointment, with or without the consent of an entity, of any receiver, liquidator, custodian, assignee, trustee, sequestrator or other similar official of an entity or any substantial part of its property; or (vi) admission by an entity in writing of its inability to pay its debts generally as they become due.

(o) "***Change of Control***" means, with respect to a Person, (i) a merger or consolidation of such Person with another Person which results in the voting securities of such Person outstanding immediately prior thereto ceasing to represent at least fifty percent (50%) of the combined voting power of the surviving Person immediately after such merger or consolidation; (ii) a transaction or series of related transactions in which another Person, together with its Affiliates, becomes the owner of fifty percent (50%) or more of the combined voting power of the outstanding securities of such Person; (iii) the sale or other transfer of all or substantially all of such Person's assets to another Person; or (iv) the stockholders or equity holders of such Person approve a plan of complete liquidation of such Person.

(p) "***Confidential Information***" means all information of whatsoever type or kind (i) provided (either directly or indirectly in writing or other tangible form or orally) by one Party (the "***Disclosing Party***") to another Party (the "***Receiving Party***") that is clearly marked and identified as "Confidential" by the Disclosing Party at the time of disclosure or (ii) specifically deemed to be "Confidential Information" pursuant to Section 14(a)(i) of this Agreement. Any information communicated orally by the Disclosing Party will be considered "Confidential Information" only if identified as such by the Disclosing Party upon such first oral disclosure. Specifically excepted from Confidential Information is all information that the Receiving Party can demonstrate by written records (1) to have been known by, or in the possession of, the Receiving Party prior to the Disclosing Party's disclosure of such Confidential Information to the Receiving Party; (2) has, after disclosure of such Confidential Information by the Disclosing Party to the Receiving Party, become known to the Receiving Party through a Third Party who is not known by the Receiving Party to be under any obligation of confidentiality to the Disclosing Party; (3) to have been part of the public domain or publicly known at the time of the Disclosing Party's disclosure of such Confidential Information to the Receiving Party; (4) has, after disclosure of such Confidential Information by the Disclosing Party to the Receiving Party, become part of the public domain or publicly known, by publication or otherwise, not due to any unauthorized act or omission by the Receiving Party; or (5) to have been independently developed by the Receiving Party without reference to, use of, or reliance upon, such Confidential Information.

(q) "***Control***" or "***Controlled***" means, with respect to an Intellectual Property right, a Party (i) owns or has a license to use and practice such Intellectual Property right and (ii) such Party has the ability to grant a license or sublicense as provided for in this Agreement under such Intellectual Property right without violating the terms of any agreement or other arrangement between such Party and either an Affiliate of such Party or a Third Party.

(r) "***Detailed Project Description***" means each written document developed and approved by the Steering Committee in accordance with Section 5(a)(ii) of this Agreement setting forth a detailed description of the Research to be performed in the conduct of the Project. The Detailed Project Description (the "***Initial Detailed Project Description***") covering the twelve-month period beginning July 1, 2011 for the Project is attached to this Agreement as Appendix B. With respect to the Initial Detailed Project Description, the Parties agree that (i) the activities specified therein to be conducted during the six-month period beginning July 1, 2011 (except for any such activities specifically identified as requiring subsequent approval by the Steering Committee) are firm and agreed to in detail by Isis and the Foundation and (ii) the activities specified therein to be conducted during the six-month period beginning January 1, 2012 have been listed for planning purposes and are therefore estimated and agreed to by the Parties in concept; those activities are subject to further approval of the Steering Committee in accordance with this Agreement prior to their conduct by Isis.

(s) "***Foundation Background Intellectual Property***" means (i) all Intellectual Property (including Intellectual Property relating to any Foundation Provided Materials but excluding the Acquirer Intellectual Property of any Acquirer of the Foundation) (A) owned by, or licensed to, the Foundation or any of its Affiliates as of the Original Effective Date or (B) acquired by, or licensed to, the Foundation or any of its Affiliates from a Third Party after the Original Effective Date and (ii) all Intellectual Property conceived, discovered, invented, made or first reduced to practice by, or on behalf of, the Foundation or any of its Affiliates after the Original Effective Date (other than (X) in the course of Isis' conduct of the Project or (Y) under the 2007 Research Agreement).

(t) "***Foundation Collaborators***" means those (i) Third Parties and Affiliates of the Foundation to which the Foundation grants the right to use all or part of the Project Deliverables, Project Intellectual Property or Project Results for HD Research and Development, including any entity collaborating with the Foundation in the conduct of HD Research and Development and/or fee-for-service laboratories or repositories providing services to the Foundation in the furtherance of the Foundation's conduct of HD Research and Development and (ii) fee-for-service laboratories providing services on behalf of any such Third Parties and Affiliates described in (i) above.

(u) "***Foundation Provided Materials***" means (i) any animal species or model (e.g., mice, rats, etc.) (including progeny derived from inbreeding and crossbreeding of any such animal species or model and unmodified derivatives of any such animal species or model and their progeny) provided to Isis by, or on behalf of, the Foundation to enable Isis to perform the Research and (ii) the physical samples of cell lines, compounds, reagents and other materials provided to Isis by, or on behalf of, the Foundation to enable Isis to perform the Research, in each case that is (A) expressly identified as a Foundation Provided Material in the Project Description or (B) otherwise agreed upon by the Steering Committee as a Foundation Provided Material for the Project.

(v) "***Foundation Provided Material Information***" means all information relating to a Foundation Provided Material that is provided to Isis by, or on behalf of, the Foundation.

(w) "***FTE***" means the equivalent of the work of one employee of Isis working on a dedicated full-time basis for one year of work (excluding vacations and holidays), consisting of at least a total of 1,820 hours per year of dedicated effort.

(x) "***General Project Description***" means the written document attached to this Agreement as Appendix A. For clarity, the General Project Description cannot be modified or amended except by the execution of a written amendment to this Agreement by an authorized signatory of each of the Parties.

(y) "***HD Field of Use***" means any activity useful for the creation, development, manufacture or distribution of a product or service for the diagnosis, treatment, cure or prevention of Huntington's disease, including the manufacture or distribution of any such product or service for sale and the sale of any such product or service.

(z) "***HD Research and Development***" means any activity useful for the creation, development, manufacture or distribution of a product or service for the diagnosis, treatment, cure or prevention of Huntington's disease, including pre-clinical testing of a product or service or, subject to Section 10(b) of this Agreement, human clinical trials involving a product or service, in all cases other than (i) the manufacture or distribution of any such product or service for sale or (ii) the sale of any such product or service. For the avoidance of doubt, HD Research and Development shall not include any right to (A) manufacture or distribute any such product or service for sale or (B) sell any such product or service; except, in each case, for pre-clinical use or, subject to Section 10(b) of this Agreement, human clinical trials.

(aa) "***Huntington***" means the human gene known as IT15 or HD (GenBank accession #NM_002111.5), or any alternative splice variants, mutants, polymorphisms and fragments thereof.

(bb) "***Huntington's disease***" or "***HD***" means the hereditary disorder caused by mutation associated with trinucleotide repeat expansion in the Huntington gene on chromosome 4p.

(cc) "***Intellectual Property***" means any discovery, invention, formulation, know-how, method, technological development, enhancement, modification, improvement, work of authorship, computer software (including, but not limited to, source code and executable code) and documentation thereof, data or collection of data, whether patentable or not, or susceptible to copyright or any other form of legal protection (e.g., trade secret).

(dd) "***Isis Background Intellectual Property***" means (i) all Intellectual Property (excluding (A) the Pre-Project Compound Intellectual Property, (B) the Acquirer Intellectual Property of any Acquirer of Isis, (C) the Isis/[***] Collaboration Intellectual Property and (D) the Regulus Intellectual Property) (1) owned by, or licensed to, Isis or any of its Affiliates as of the Original Effective Date or (2) acquired by, or licensed to, Isis or any of its Affiliates from a Third Party after the Original Effective Date and (ii) all Intellectual Property conceived, discovered, invented, made or first reduced to practice by, or on behalf of, Isis or any of its Affiliates after the Original Effective Date (other than (X) in the course of Isis' conduct of the Project or (Y) under the 2007 Research Agreement).

(ee) "***Isis Provided Materials***" means any animal species or model (e.g., mice, rats, etc.) (including progeny derived from inbreeding and crossbreeding of any such animal species or model and unmodified derivatives of any such animal species or model and their progeny) and the physical samples of compounds, reagents, cell lines and other materials acquired by Isis from a Third Party to enable Isis to perform the Research.

(ff) "***Isis Provided Reimbursable Materials***" means each Isis Provided Material that is (i) expressly identified as an Isis Provided Reimbursable Material in the Project Description or (ii) otherwise agreed upon by the Steering Committee (as defined in Section 5(a)(i) of this Agreement) as an Isis Provided Reimbursable Material for the Project.

(gg) "***Isis/[***] Collaboration Intellectual Property***" means all Intellectual Property conceived, discovered, invented, made or first reduced to practice by, or on behalf of, Isis or [***] under (i) that certain Collaborative Research Agreement, dated [***], between Isis and [***] and/or (ii) that certain Amended and Restated Collaborative Research Agreement, dated [***] between Isis and [***].

(hh) "***MOE Gapmer***" means a single-stranded ASO of less than 25 nucleotides comprising a region of at least 6 unsubstituted 2' deoxy nucleotides with the remaining nucleotides having a 2'-O-(methoxyethyl) substitution at the 2' position.

(ii) "***Patent Expenses***" means, with respect to either Party, all out-of-pocket costs and expenses (including attorneys' fees and government filing fees) incurred by that Party in accordance with Section 9(d) of this Agreement in connection with the preparation, review, filing, prosecution and maintenance of the appropriate filings and issued patents, including any extensions or supplemental protection certificates thereto, to protect the Parties' rights in any Patentable Project HD Intellectual Property.

(jj) "***Patentable Project HD Intellectual Property***" means any Project HD Intellectual Property which is or may be patentable or otherwise protectable under Title 35 U.S.C. and corresponding legislation in other jurisdictions.

(kk) "***Person***" means any individual, corporation, company, partnership, trust, limited liability company, association or other business entity.

(ll) "***Pre-Project Compound***" means all MOE Gapmers identified by Isis prior to the Original Effective Date in the course of Isis' conduct of research activities pursuant to that certain Research Agreement, dated as of August 1, 2006, entered into between Isis and the Foundation which (i) Isis used in the conduct of the 2007 Research Agreement Project or (ii) are used in Isis' conduct of the Project.

(mm) "***Pre-Project Compound Intellectual Property***" means any Intellectual Property in or relating to a Pre-Project Compound.

(nn) "***Project***" means (i) the programs of Research performed by, or on behalf of, Isis as described in the Additional Project Activities Description together with (ii) the program of Research to be performed by Isis as described in the Project Description.

(oo) "***Project Compound***" means all (i) Pre-Project Compounds, (ii) 2007 Research Agreement Project Compounds or (iii) MOE Gapmers that are identified by Isis in the course of Isis' conduct of the Project, including any Project Human Compound. For the avoidance of doubt, Pre-Project Compounds will be Project Compounds for all purposes under this Agreement.

(pp) "***Project Deliverable***" means (i) those Project Reports (as defined in Section 5(e) of this Agreement), those FTE Reports (as defined in Section 5(e) of this Agreement) and other items set forth in the Project Description which are to be delivered by Isis to the Foundation in connection with the conduct of the Project by Isis, (ii) those Approved Foundation Requested Project Compounds which are to be delivered by Isis to the Foundation pursuant to Section 8(c) of this Agreement and (iii) any other item or material otherwise agreed to be such by the Steering Committee.

(qq) "***Project Description***" means the General Project Description together with the Detailed Project Descriptions for the Project.

(rr) "***Project HD Intellectual Property***" means any Project Intellectual Property that (i) claims the composition of matter of a Project Compound and/or a method of using a Project Compound for the treatment of Huntington's disease or (ii) is necessary or useful for the creation, development, manufacture or distribution of a product or service for the diagnosis, treatment, cure or prevention of Huntington's disease.

(ss) "***Project Human Compound***" means any Project Compound that modulates the expression of Huntington and acts predominantly by hybridizing to mRNA or pre-mRNA in humans.

(tt) "***Project Intellectual Property***" means all (i) Pre-Project Compound Intellectual Property, (ii) 2007 Research Agreement Project Intellectual Property and (iii) Intellectual Property conceived, discovered, invented, made or first reduced to practice in the course of Isis' conduct of the Project other than any such Intellectual Property that constitutes Isis Background Intellectual Property or Foundation Background Intellectual Property.

(uu) "***Project Non-HD Intellectual Property***" means any Project Intellectual Property that does not constitute Project HD Intellectual Property.

(vv) "***Project Non-Human Compound***" means any Project Compound that does not constitute a Project Human Compound.

(ww) "***Project Results***" means all (i) 2007 Research Agreement Project Results and (ii) all data, formulae, methods, outcomes, protocols or other results produced in the course of Isis' performance of the Research.

(xx) "***Provided Research Materials***" means (i) those Isis Provided Reimbursable Materials for which the Foundation has reimbursed Isis in accordance with Section 6(b)(i) of this Agreement and (ii) the Foundation Provided Materials for the Project.

(yy) "***Regulus***" means (i) Regulus Therapeutics Inc. and (ii) the successor Person of any Change of Control directly or indirectly involving Regulus Therapeutics Inc.

(zz) "***Regulus Intellectual Property***" means all Intellectual Property owned by, or licensed to, Regulus.

(aaa) "***Research***" means all of the activities undertaken by, or on behalf of, Isis under this Agreement to conduct and complete the Project.

(bbb) "***Research FTE***" means an FTE (or a fractional unit thereof) that has been designated to perform the Research.

(ccc) "***Research FTE Rate***" means, for all Research FTEs (on a quarterly basis), an amount equal to US$[***] per Research FTE per quarter (equivalent to an annual Research FTE Rate of US$[***]).

(ddd) "***Research and Development***" means any activity useful for the creation, development, manufacture or distribution of a product or service, including pre-clinical testing of a product or service or, subject to Section 10(b) of this Agreement, human clinical trials involving a product or service, in all cases other than (i) the manufacture or distribution of any such product or service for sale or (ii) the sale of any such

product or service. For the avoidance of doubt, Research and Development will not include any right to (1) manufacture or distribute any such product or service for sale or (2) sell any such product or service; except, in each case, for pre-clinical use or, subject to Section 10(b) of this Agreement, human clinical trials.

(eee) "***Third Party***" means any Person other than a Party or its Affiliates.

Research; Project

2. Number of Research FTEs; Utilization of Research FTEs.

(a) Number of Research FTEs.

(i) Initial Number of Research FTEs. Beginning on the Effective Date, Isis will provide [***] Research FTEs to perform the Research. The Parties acknowledge and agree that the number of then-current Research FTEs performing the Research will only be subject to adjustment as provided in Section 2(a)(ii) of this Agreement.

(ii) Changes in the Number of Research FTEs. The number of Research FTEs performing Research may only be increased or decreased above the then-current number of Research FTEs required to be provided by Isis to perform the Research by the agreement of the Steering Committee; *provided, that*, (A) at no time will the number of Research FTEs performing the Research exceed [***] ([***]) Research FTEs (the "***Research FTE Maximum Number***") and (B) any increase in the number of Research FTEs may only be for the fixed period of time set forth in the applicable Steering Committee meeting minutes. Any agreed upon increase or decrease in the then-current number of Research FTEs required to be provided by Isis to perform the Research will occur within a period of time mutually agreed upon by the Steering Committee. The Parties acknowledge and agree that the Research FTE Maximum Number may only be increased by the execution of a written amendment to this Agreement by an authorized signatory of each of the Parties.

(b) Utilization of Research FTEs. Isis and the Foundation agree that each individual being provided by Isis to constitute all or a part of a Research FTE may (i) devote less than 100% of his or her full-time effort to perform the Research and (ii) perform activities of any type or nature for Isis or any Third Party; *provided, that*, the time spent by any such individual performing such non-Project activities will not be taken into account for any purpose under this Agreement (including for purposes of calculating (A) the number of Research FTEs being provided by Isis under this Agreement or (B) the amount of any payment owed by the Foundation under this Agreement). Similarly, Isis may satisfy its Research FTE obligations hereunder by having multiple individuals contribute toward one full Research FTE.

3. Performance of the Research; Limited Right to Subcontract the Research; Certain Notifications Relating to the Project; Experimental Nature of the Research.

(a) Performance of the Research; Limited Right to Subcontract the Research.

(i) Performance of the Research. Isis agrees that (A) each Research FTE will perform the Research in accordance with this Agreement, including the Project Description and (B) no Research shall be performed except as expressly set forth in the Project Description or otherwise approved by the Steering Committee. During the Term (as defined in Section 17(a) of this Agreement), unless otherwise explicitly agreed to by the Steering Committee or expressly provided for in the Project Description, Isis will

also provide such other resources (including all necessary administrative and support personnel, equipment, tools, Isis Provided Materials and supplies) and effort as is commercially reasonable to perform the Research in accordance with this Agreement, including the Project Description.

(ii) Limited Right to Subcontract the Research. The Parties acknowledge and agree that Isis may (A) sub-contract those activities which are expressly set forth in the Project Description or otherwise agreed upon by the Steering Committee as activities to be sub-contracted (such activities, "***Subcontracted Research***") and (B) sub-contract such Subcontracted Research to the Third Party set forth in the Project Description or otherwise agreed upon by the Steering Committee as the Third Party or Affiliate to conduct such sub-contracted activities (each such Third Party or Affiliate, a "***Subcontractor***"). Isis agrees that (1) all Subcontracted Research shall be performed pursuant to a written agreement between Isis and the Subcontractor performing such Subcontracted Research upon terms and conditions that a) are consistent with the terms and conditions of this Agreement and b) do not conflict with Isis' obligations or the Foundation's rights under this Agreement and (2) Isis shall cause each Subcontractor to conduct the Subcontracted Research in accordance with, and subject to, the terms and conditions of such agreement. Upon the Foundation's request, Isis will provide the Foundation with copies of such agreements between Isis and any such Subcontractor. Isis further agrees that Isis shall be solely responsible and liable to CHDI under this Agreement for the Subcontracted Research conducted by each Subcontractor as if such Research were conducted by Isis.

(b) Certain Notifications Relating to the Research.

(i) Change of Circumstances Notices. If at any time following the Effective Date Isis makes a good faith determination that, (A) the Research cannot be conducted and completed substantially in accordance with this Agreement and the Project Description; (B) the Research (or any portion thereof) cannot be substantially completed within the estimated time frame set forth in the Project Description; or (C) the continued performance of the Research in accordance with this Agreement and the Project Description (1) is unlikely to yield scientifically valid or useful results, (2) will violate any applicable federal, state, local, international, health authority and institutional laws, rules, regulations, orders or guidelines, or (3) will violate principles of ethics or scientific

integrity, Isis will promptly give written notice (each, a "***Change of Circumstances Notice***") to the Foundation. Each Change of Circumstances Notice will set forth a detailed description of Isis' determination (including the facts and circumstances underlying such determination and Isis' basis for such determination). Following the delivery of a Change of Circumstances

Notice, Isis will, at the request of the Foundation, promptly make senior officers and appropriate scientific or technical personnel reasonably available to the Foundation to discuss the basis for Isis' determination.

(ii) **Post-Effective Date Knowledge Notice.** If at any time following the Effective Date Isis acquires knowledge that would render one or more of the representations and warranties set forth in Section 16(b) of this Agreement untrue or incorrect if such representation or warranty were based upon Isis' knowledge at such time (instead of being based upon Isis' knowledge as of the Effective Date), Isis will promptly give written notice (each, a "***Post-Effective Date Knowledge Notice***") to the Foundation. Each Post-Effective Date Knowledge Notice will set forth a detailed description of the facts and circumstances relating to the applicable representation or warranty (including details as to Isis' basis for determining that such representation or warranty would no longer be true and correct). Following the delivery of a Post-Effective Date Knowledge Notice, Isis will, at the request of the Foundation, promptly make senior officers and appropriate scientific or technical personnel reasonably available to the Foundation to discuss (A) the facts and circumstances related to the subject matter of such Post-Effective Date Knowledge Notice and (B) potential courses of action to address such matter.

(c) **Experimental Nature of the Research.** The Foundation acknowledges that (i) the Research is of an experimental and developmental nature and (ii) Isis cannot guarantee that the objectives of the Research will be achieved or that the performance of the Research will yield any specific deliverables, results or Intellectual Property.

4. **Obligation to Provide Foundation Provided Materials and Foundation Provided Material Information; Reimbursement for Isis Provided Reimbursable Materials; Use and Ownership of Provided Research Materials and Foundation Provided Material Information; Retention of Provided Research Materials; Risk of Loss of Provided Research Materials; Specialized Licenses or Services.**

(a) **Obligation to Provide Foundation Provided Materials and Foundation Provided Material Information.** The Foundation will provide Isis with (i) each Foundation Provided Material designated as a Foundation Provided Material for the Project and (ii) any information in respect of each such Foundation Provided Material that is reasonably necessary to enable Isis to use such Foundation Provided Material in the performance of the Research so long as such information is in the possession of the Foundation and the Foundation is permitted to provide such information to Isis without breaching any obligation to any Third Party.

(b) **Reimbursement for Isis Provided Reimbursable Materials.** The Foundation will, in accordance with Section 6(b)(i) of this Agreement, reimburse Isis for the actual costs incurred by Isis to procure each Isis Provided Reimbursable Material

designated as an Isis Provided Reimbursable Material for the Project (up to [***]% of the estimated cost of such Isis Provided Reimbursable Material as is set forth in the Project Description or the applicable mutually-approved Steering Committee meeting minutes). Isis agrees that (i) each Isis Provided Reimbursable Material shall be procured pursuant to a written agreement between Isis and the Third Party or Affiliate providing such Isis Provided Reimbursable Material upon terms and conditions that (A) are consistent with the terms and conditions of this Agreement and (B) do not conflict with Isis' obligations or the Foundation's rights under this Agreement and (ii) Isis shall cause each Third Party or Affiliate providing Isis Provided Reimbursable Materials to provide such Isis Provided Reimbursable Materials in accordance with, and subject to, the terms and conditions of such agreement. Upon the Foundation's request, Isis will provide the Foundation with copies of such agreements between Isis and any such Third Party or Affiliate.

(c) **Use and Ownership of Provided Research Materials and Foundation Provided Material Information; Retention of Provided Research Materials; Risk of Loss of Provided Research Materials.**

(i) **Use and Ownership of Provided Research Materials and Foundation Provided Material Information.** Isis agrees that the Provided Research Materials and the Foundation Provided Material Information (A) will be used by Isis for the sole purpose of conducting the Project and for no other purpose, (B) will be used, handled, stored and disposed of in compliance with all applicable laws, regulations and rules and (C) will not be transferred to any Third Party or to any Affiliate of Isis except (1) as expressly required or contemplated by this Agreement (e.g., to a Subcontractor in accordance with Section 3(a)(ii) of this Agreement) or (2) pursuant to the written request of an authorized representative of the Foundation. Except to the extent expressly required by the Project Description, Isis further agrees that it will not: (a) directly or indirectly, reverse engineer, deconstruct or in any way analyze or determine the identity, structure or composition of any Foundation Provided Materials or the properties thereof (chemical, biochemical, physical, biological or other); b) use any Provided Research Materials in any human; or c) export any Provided Research Materials or Foundation Provided Material Information in any manner that would violate any applicable export law or regulation, including the United States. Isis acknowledges and agrees that (a) as between Isis and the Foundation, the Foundation owns the Provided Research Materials and Foundation Provided Material Information and (b) Isis will not, pursuant to this Agreement, acquire any ownership or other interest in any Provided Research Materials or Foundation Provided Material Information.

(ii) **Retention of Provided Research Materials.** Except for live animals and animal-derived materials (e.g., tissue samples) that require consistent care or maintenance, Isis will retain all unused Provided Research Materials for a period of [***] following the earlier to occur of (A) the completion or cancellation of the Project or (B) the expiration or termination of this Agreement (such period, the "***Provided Research Materials Retention Period***"). Except with respect to any Isis Provided Reimbursable Material for which, prior to Isis' purchase of such Isis Provided Reimbursable Material, the Foundation provided written consent that Isis is not required to provide such Isis Provided Reimbursable Material to the Foundation, during the Provided Research Materials Retention Period, Isis will, at the Foundation's request and expense, ship all or part of any or all of the unused Provided Research Materials to the Foundation or to such Third Party as the Foundation will direct in writing. Upon the expiration of the Provided Research Materials Retention Period, Isis will appropriately discard or destroy all such unused Provided Research Materials.

(iii) **[***] of Provided Research Materials.** Immediately upon Isis' receipt of a Provided Research Material and continuing until such Provided Research Material is delivered or disposed of by Isis pursuant to this Agreement (the "***Handling Period***"), Isis will [***], and will be [***], all [***], (A) [***] such Provided Research Material and (B) any preparation for shipment and shipment of such Provided Research Material pursuant to this Agreement, in all cases to the extent each such Provided Research Material is [***]. If a Provided Research Material that is not [***] is [***], the Parties will [***] such Provided Research Material. Isis will use commercially reasonable efforts to obtain and maintain [***] during the Handling Period [***] each Provided Research Material.

(d) **Reimbursement for Specialized Licenses or Services.** The Foundation will, in accordance with Section 6(b)(ii) of this Agreement, reimburse Isis for the actual costs incurred by Isis to license or procure from a Third Party or one of its Affiliates, as the case may be, each license or service that is expressly identified as a license or service the costs of which are to be reimbursed by the Foundation in (i) the Project Description or (ii) otherwise agreed upon by the Steering Committee as a license or service the costs of which are to be reimbursed by the Foundation for the Project (up to [***]% of the estimated cost of such license or service as is set forth in the Project Description or the applicable mutually-approved Steering Committee meeting minutes) (any such license or service hereinafter referred to as a "***Specialized License or Service***"). Isis agrees that (A) each Specialized License or Service shall be licensed or procured pursuant to a written agreement between Isis and the Third Party or Affiliate licensing or providing such Specialized License or Service upon terms and conditions that (1) are consistent with the terms and conditions of this Agreement and (2) do not conflict with Isis' obligations or the Foundation's rights under this Agreement and

(B) Isis shall cause each Third Party or Affiliate providing a Specialized License or Service to provide such Specialized License or Service in accordance with, and subject to, the terms and conditions of such agreement. Upon the Foundation's request, Isis will provide the Foundation with copies of such agreements between Isis and any such Third Party or Affiliate.

Research/Project Management

5. **Steering Committee; Project Managers; Limited Authority of the Steering Committee and Project Managers; Recordkeeping; Project Reports.**

(a) **Steering Committee.**

(i) **Establishment and Make-Up of the Steering Committee; External Advisors.**

(A) **Establishment and Make-Up of the Steering Committee.** Within a reasonable period of time following the Effective Date, not to exceed 30 days, the Parties will establish a committee (the "***Steering Committee***"). The Steering Committee will be comprised of four members. Each Party will designate two members of the Steering Committee. Each Party will appoint members who possess appropriate qualifications to conduct the responsibilities of the Steering Committee. Each Party may also, from time to time, invite other of its personnel to attend the Steering Committee meetings; *provided, that*, such other personnel will (1) act in an advisory, non-voting capacity only and (2) not be entitled to decide or approve any matter requiring decision by or approval of the Steering Committee. A Party may at any time replace one or both of its members of the Steering Committee upon written notice to the other Party. The Steering Committee, as a formal governing body under this Agreement, will be dissolved upon the expiration of the Term.

(B) **External Advisors.** The Steering Committee may, from time to time, identify and appoint Third Party experts to advise the Steering Committee on technical and other matters; *provided, that*, such experts will (1) act in an advisory, non-voting capacity only and will not be entitled to decide or approve any matter requiring decision by or approval of the Steering Committee and (2) be required to abide by confidentiality and non-use obligations at least as restrictive as those set forth in Section 14 of this Agreement in respect of Confidential Information to which such experts are granted access.

(ii) **Responsibilities of the Steering Committee; Scope and Content of Detailed Project Descriptions.**

(A) **Responsibilities of the Steering Committee.** The Steering Committee will have the authority to make decisions about those matters that, by the express terms of this Agreement, are to be addressed by the Steering Committee. In addition to any other matter that, by the express terms of this Agreement are to be determined by the Steering Committee, the Steering Committee will be responsible for each of the following matters: (1) on at least a quarterly basis, reviewing the Detailed Project Description for the Project and, if deemed reasonably necessary by the Steering Committee, refining, updating and approving the Detailed Project Description for the Project for the 12-month period beginning on the date such Detailed Project Description is so updated and approved by the Steering Committee (each such Detailed Project Description to be developed in accordance with, and set forth the information specified in, Section 5(a)(ii)(B) of this Agreement), *provided, that*, the Parties shall use their respective commercially reasonable efforts to facilitate the approval

by the Steering Committee of (and the Steering Committee will diligently endeavor to approve) at least two calendar quarters of Research activities; (2) on at least a quarterly basis, subject to Section 2 of this Agreement, reviewing and, if deemed reasonably necessary by the Steering Committee, approving changes to the number of Research FTEs (not to exceed the Research FTE Maximum Number) to be provided by Isis to perform the Research, *provided, that*, the Parties shall use their respective commercially reasonable efforts to facilitate the approval by the Steering Committee of (and the Steering Committee will diligently endeavor to approve) the requisite number of Research FTEs to be provided by Isis to conduct the approved Research activities for at least two calendar quarters; (3) monitoring the coordination, implementation and conduct of the Project in accordance with the Project Description; (4) reviewing the status and progress of the conduct of the Project; (5) determining if changes are needed to the scope of the Project; (6) implementing any changes to the scope of the Project that have been approved by the Parties; (7) reviewing and discussing the Invention Notices (as defined in Section 9(c)(i) of this Agreement) in respect of the Project Intellectual Property; (8) reviewing and discussing the filing of any patent applications in respect of any Patentable Project Intellectual Property; (9) reviewing and discussing the Project Deliverables, Project Results and such other matters related to this Agreement and the Research as are reasonably requested by either of the Parties; (10) facilitating Isis'

consideration of any Foundation Project Compound Request Notice submitted by the Foundation under Section 8(c) of this Agreement; and (11) facilitating on-going communications between the Parties. Notwithstanding the provisions of Section 5(a)(iii)(B) below, if the Steering Committee is unable to reach consensus regarding the activities to be included and performed in the Detailed Project Description (including without limitation, an inability to reach consensus regarding the Research activities for the next calendar quarter), the matter will first be submitted to B. Lynne Parshall, in the case of Isis (or such other individual identified in writing by Isis), and Robi Blumenstein, in the case of the Foundation (or such other individual identified in writing by the Foundation) within five days for resolution and any such resolution will be deemed to be a decision and approval by the Steering Committee for purposes of this Agreement.

(B) **Scope and Content of Detailed Project Descriptions.** Each Detailed Research Project Description developed and approved by the Steering Committee for the Project will be consistent with the scope of the Project as outlined in the General Project Description. The Detailed Project Description for the Project will include the following information: (1) a reasonably detailed description (including the details of all material scientific protocols) of the Research activities and the timing thereof to be undertaken during the period covered by such Detailed Project Description (all such Research activities to be consistent with the scope of the Project as outlined in the Project Description); (2) an estimated time frame for the completion of the Project; (3) a breakdown of the number of Research FTEs to be allocated to the conduct of the Project during the period covered by such Detailed Project Description; (4) a list of each Subcontractor together with a reasonably detailed description of the Subcontracted Research to be undertaken by each such Subcontractor in the conduct of the Project during the period covered by such Detailed Project Description; (5) a list of the Foundation Provided Materials to be provided for the conduct of the Project (including the amount and estimated cost thereof); (6) a list of any Isis Provided Reimbursable Materials required for the conduct of the Project (including the amount and estimated cost thereof); (7) a list of any Specialized Licenses or Services required for the conduct of the Project (including the cost thereof); and (8) such other information as may be necessary to appropriately describe the Research activities to be undertaken in the conduct of the Project during the period covered by such Detailed Project Description.

(iii) **Operating Procedures of the Steering Committee; Decisions by the Steering Committee; Steering Committee Minutes; Resolution of Steering Committee Disputes.**

(A) **Operating Procedures of the Steering Committee; Decisions by the Steering Committee; Steering Committee Minutes.** The Steering Committee will establish its own internal operating procedures and meeting schedule (such meetings to be held in person or by video or telephone conference as mutually agreed upon by the Steering Committee members); *provided, however*, the Steering Committee will meet on a face-to-face basis at least once every calendar quarter following Isis' delivery of the Project Report for the preceding calendar quarter in accordance with Section 5(e)(i) of this Agreement. Each Party may, as it deems reasonably necessary, call ad-hoc meetings of the Steering Committee by providing reasonable notice to the other Party. Any activity or matter that requires a decision by, or the approval of, the Steering Committee under this Agreement will require the affirmative consent of each member of the Steering Committee and will only be a valid and binding decision and/or approval of the Steering Committee if such decision and/or approval is expressly identified in the applicable mutually-approved Steering Committee meeting minutes. At each meeting of the Steering Committee, one meeting attendee will be appointed to record and, within a period of 30 days after each such meeting, distribute the minutes of such meeting to the Steering Committee members for approval (the approval of the content of each such meeting minutes to be evidenced by the initialing of such meeting minutes by at least one of each Party's designated Steering Committee members).

(B) **Resolution of Steering Committee Disputes.** If the Steering Committee cannot reach consensus on any activity or matter that requires a decision by, or the approval of, the Steering Committee (each, a "***Steering Committee Dispute***"), either Party may, within 30 days after the Steering Committee Dispute arises, submit such Steering Committee Dispute to B. Lynne Parshall, in the case of Isis (or such other individual identified in writing by Isis), and Robi Blumenstein, in the case of the Foundation (or such other individual identified in writing by the Foundation), for resolution by providing a written notice (each, an "***Internal Steering Committee Dispute Resolution Notice***") to the other Party setting forth in reasonable detail the basis of such dispute. Such individuals will, within 20 days after such Internal Steering Committee Dispute Resolution Notice is delivered, meet and attempt in good faith to resolve such Steering Committee Dispute.

If such Steering Committee Dispute is not resolved within such 20-day period, either Party may require that the Parties submit such Steering Committee Dispute for resolution by an independent Third Party with appropriate qualifications for resolution to evaluate such matter (a "***Neutral Expert***") by providing a written notice (an "***External Steering Committee Dispute Resolution Notice***") to such effect that identifies the Steering Committee Dispute to be resolved. If the Parties fail to agree on a Neutral Expert within 10 days after an External Steering Committee Dispute Resolution Notice is delivered, then each Party will submit the name and qualifications of one proposed Neutral Expert, along with a written statement not to exceed five pages that identifies the issue(s) to be decided, to JAMS in Denver, Colorado, with a copy to the other Party, and JAMS will appoint a single arbitrator, who will be authorized solely to select, within 10 days of his or her appointment and pursuant to this Section 5(a)(iii)(B), which Party's proposed Neutral Expert will be designated for resolution of such matter, which decision will be final and binding on both Parties. Upon the designation of the Neutral Expert, each Party will have 15 business days from the date of the designation of such Neutral Expert to submit any appropriate materials to such Neutral Expert, with copies to the other Party. No Party will communicate with the Neutral Expert except by written communications copied to the other Party, or orally in the physical or telephonic presence of the other Party. The Neutral Expert will render a written decision within 15 days after the deadline for submission of materials from the Parties. The decision of the Neutral Expert will be final and binding on both Parties; *provided, however*, in no event will either Party be obligated to violate any applicable federal, state, local, international, health authority and institutional laws, rules, regulations, orders or guidelines. The Parties agree that any and all such deliberations will be confidential.

(b) Project Managers.

(i) Appointment of the Project Managers; Operating Procedures of the Project Managers. Within a reasonable period of time following the Effective Date, not to exceed 30 days, each Party will appoint a project manager (each, a "***Project Manager***") to oversee the day-to-day coordination, implementation and performance of the Research. The Project Managers will establish their own operating procedures and meeting schedule (such meetings to be held in person or by video or telephone conference as mutually agreed upon by the Project Managers); *provided, however*, the Project Managers will meet on a bi-weekly basis or at such other frequency as agreed upon by the Project Managers. Isis'

Project Manager will keep the Foundation's Project Manager fully informed as to the status and progress of the conduct of the Project (including the status of the completion time frame of the Project as compared to the estimated completion time frame specified in the Project Description) and such other matters related to this Agreement and the Research as are reasonably requested by the Foundation's Project Manager. Upon the expiration of the Term, each Party's obligation to have and maintain a Project Manager under this Agreement will terminate.

(ii) Responsibilities of the Project Managers. The Project Managers will be responsible for the following activities: (A) assisting the Steering Committee in the development of the revised Detailed Project Descriptions for the Project (each such Detailed Project Description to be developed in accordance with, and set forth the information specified in, Section 5(a)(ii)(B) of this Agreement); (B) overseeing the coordination, implementation and conduct of the Project in accordance with the Project Description; (C) reviewing the status and progress of the conduct of the Project; (D) determining if changes are needed to the scope of the Project; (E) implementing any changes to the scope of the Project that have been approved by the Parties; (F) reviewing and discussing the Project Deliverables, Project Results and such other matters related to this Agreement and the Research as are reasonably requested by either of the Parties; and (G) facilitating on-going communications between the Parties.

(c) Limited Authority of the Steering Committee and Project Managers. For the avoidance of any doubt, the Parties agree that neither the Steering Committee nor any Project Manager will have the power or authority to (i) modify or make any amendments to this Agreement, (ii) except as otherwise provided in Section 5(a)(ii)(A) of this Agreement, modify or make any amendments to the Project Description, (iii) waive a Party's rights under, or compliance with, this Agreement or (iv) determine whether there has been a breach of a Party's obligations pursuant to this Agreement.

(d) Recordkeeping. Isis will keep complete and accurate records of the Research performed by it under this Agreement and of all Project Deliverables, Project Intellectual Property and Project Results. Isis will retain all such records, including all raw data, for a period of not less than [***] following the date of the expiration or termination of the Term. During the Term of this Agreement and such [***] period, such records (including the relevant pages of all applicable laboratory notebooks containing data, information or notations relating to the performance of the Research) will, upon 10 business days prior written notice from the Foundation, be available at Isis' facilities at all reasonable times during normal business hours for inspection, examination or copying by, or on behalf of, the Foundation at the Foundation's expense, or alternatively, at Isis' election, will be made available to the Foundation in electronic form at the Foundation's

expense. During the [***] period following the date of the expiration or termination of the Term, Isis will, at the Foundation's request and expense, ship copies of all or part of such records to the Foundation or to such Third Party as the Foundation will direct in writing. Notwithstanding the foregoing, Isis may retain copies of all such records to allow Isis to exercise its rights and satisfy any of its obligations under this Agreement.

(e) Project Reports; FTE Reports.

(i) **Project Reports.** Isis will deliver to the Foundation (A) a written report on the performance of the Research within [***] after the end of each [***] during the conduct of the Project and continuing until the cancellation or completion of the Project, together with any additional reports specified in the Project Description (collectively, the "[***] ***Project Reports***"), and (B) a final written report on the conduct of the Project (the "***Final Project Report***" and, together with the [***] Project Reports, the "***Project Reports***") within [***] of the [***]. Each Project Report will address each of the following in substantially the same format and containing the same degree of detail as Isis generally uses to communicate such information internally and to its Third Party research collaborators: (1) a summary of the status and progress of the Project (including an update on the projected time frame for the completion of the Project), (2) material developments and issues relating to the conduct of the Project and (3) a summary of any Project Results produced during the period covered by the Project Report. Each Project Report will include a copy of (a) each report related to the Research activities received by Isis during the period from a Third Party or Affiliate and (b) all final versions of written documents created by Isis summarizing the Project Results for the Research activities and not otherwise included in the any of the reports described in (a) above that are or have been previously delivered to the Foundation.

(ii) **FTE Reports.** Isis will deliver to the Foundation Research FTE reports (each, a "***FTE Report***") on a [***] basis (each such FTE Report to be delivered at least [***] prior to the Steering Committee's regularly scheduled meeting for the period covered by such FTE Report) for each [***] through the [***]. Each FTE Report will contain [***].

(f) **Follow-Up Queries.** Isis will provide the Foundation's Steering Committee members with a reasoned response (including, if requested by a Foundation Steering Committee member, the raw data underlying the Project Results or the Additional Project Activities Project Results) to any follow-up scientific questions asked by a Foundation Steering Committee member concerning (i) the Research that is the subject of a Project Report or arises from a discussion at a Steering Committee meeting or (ii) the Additional Project Activities that are the subject of a Project Report or arises from a discussion at a Steering Committee meeting.

Any requested raw data may be provided to the Foundation in the same format (e.g., electronic transfer, CD, DVD, SAS, Microsoft Excel spreadsheet, etc.) as is used by Isis for its own purposes.

Payments

6. **General Payment Obligation; Reimbursement Obligation for Isis Provided Reimbursable Materials Costs, Specialized Licenses or Services Costs and Shipping and Insurance Costs; Quarterly Research Payments; Conditions Precedent for the Payments; Invoicing; Payment Remittance.**

(a) **General Payment Obligation.** In full consideration of Isis' performance of the Research and its other obligations under this Agreement, the Foundation will, subject to the terms and conditions set forth in this Agreement, make payments to Isis as provided in this Agreement. The calculation of the amount of such payments, the timing of the payment of such payments and conditions precedent for the payment of such payments are set forth in this Section 6.

(b) **Reimbursement Obligation for Isis Provided Reimbursable Materials Costs, Specialized Licenses or Services Costs and Shipping and Insurance Costs.**

(i) **Isis Provided Reimbursable Materials Costs.** Subject to Section 4(b) of this Agreement, the Foundation will reimburse Isis for the actual costs incurred by Isis to procure any Isis Provided Reimbursable Materials (all such costs hereinafter referred to as the "***Isis Provided Reimbursable Materials Costs***").

(ii) **Specialized Licenses or Services Costs.** Subject to Section 4(d) of this Agreement, the Foundation will reimburse Isis for the actual costs incurred by Isis to license or procure any Specialized Licenses or Services (all such costs hereinafter referred to as the "***Specialized Licenses or Services Costs***").

(iii) **Shipping and Insurance Costs.** The Foundation will reimburse Isis for (A) the actual costs of carriage, customs duties and insurance incurred by Isis in connection with the delivery of the Project Deliverables and Provided Research Materials to the Foundation (or such Third Party specified by the Foundation) and (B) for the actual costs and expenses incurred by Isis in connection with the shipping of the Project Deliverables and Provided Research Materials to the Foundation (or such Third Party specified by the Foundation) (all such costs hereinafter referred to as the "***Shipping and Insurance Costs***"), in each case provided that such costs are reasonable.

(c) **Additional Project Activities Description Payment.** For the performance of the Research performed by, or on behalf of, Isis as described in the Additional Project Activities Description (the "***Additional Project Activities***"), the Foundation will make a one-time payment (the "***Additional Project Activities Payment***") to Isis in the amount of US$[***] (the "***Additional Project Activities Payment Amount***"). Isis agrees that (i) upon the payment of the Additional Project Activities Payment Amount by the Foundation, the Foundation will have paid Isis all amounts owed by the Foundation to Isis for the conduct of the Additional Project Activities and (ii) the Foundation has paid Isis all amounts owed by CHDI pursuant to Section 5 of the 2007 Research Agreement.

(d) **Advance Research Payment.** The Foundation will make a payment (the "***Advance Research Payment***") to Isis in the amount of US$[***] (the "***Advance Research Payment Amount***"). Isis acknowledges and agrees that the Advance Research Payment Amount shall, in accordance with Section 6(g)(i) of this Agreement, be applied as a credit against the final Quarterly Research Payment (as defined in Section 6(e) of this Agreement).

(e) **Quarterly Research Payments.**

(i) **General.** Promptly following the end of each calendar quarter, Isis will calculate the payment (each, a "***Quarterly Research Payment***") to be made by the Foundation in respect of (A) the Research FTE costs incurred by Isis in performing the Research during such period, (B) Isis Provided Reimbursable Materials Costs incurred by Isis during such period, (C) the Specialized Licenses or Services Costs incurred by Isis during such period and (D) the Shipping and Insurance Costs incurred by Isis during such period.

(ii) **Specific Calculation of each Quarterly Research Payment.** Each Quarterly Research Payment in respect of the period covered by such Quarterly Research Payment will be calculated in accordance with the terms of this Agreement and will be an amount equal to [***].

(f) **Conditions Precedent for Payments.**

(i) **Conditions Precedent for the Payment of the Additional Project Activities Payment.** The obligation of the Foundation to pay the Additional Project Activities Payment is subject to Isis' delivery to the Foundation, in accordance with [***] of this Agreement, of [***] on or prior to the date that Isis issues an invoice in respect of such Additional Project Activities Payment.

(ii) **Conditions Precedent for the Payment of the Quarterly Research Payments.** With respect to each Quarterly Research Payment, the obligations of the Foundation to pay such Quarterly Research Payment are subject to the fulfillment of each of the following conditions:

[***]

provided, however, that the Foundation will pay each Quarterly Research Payment to Isis no later than [***] after the date of the Foundation's receipt of the invoice for such Quarterly Research Payment, if Isis has, with respect to such Quarterly Research Payment [***].

(g) **Invoicing; Payment Remittance.**

(i) **Invoicing.** At such time as Isis has, in accordance with [***] of this Agreement, delivered to the Foundation the [***], Isis will also deliver to the Foundation an invoice for the Additional Project Activities Payment to be made by the Foundation for such period. At such time as Isis has, in accordance with Section 5(e) of this Agreement, delivered to the Foundation the [***] and [***] for a particular calendar quarter, Isis will also deliver to the Foundation an invoice for the Quarterly Research Payment to be made by the Foundation for such calendar quarter. Each invoice delivered by Isis for a payment under this Agreement will (A) reference the "RecID" number set forth in the footer of this Agreement, (B) be issued in US Dollars, (C) be itemized and contain detailed information in respect of the payment being billed under such invoice and (D) as applicable, include a copy of all relevant receipts and/or invoices related to the payment being billed under such invoice. Isis agrees that a) the invoice submitted by Isis in respect of the final Quarterly Research Payment shall credit the Advance Research Payment Amount against such final Quarterly Research Payment and b) if the amount of final Quarterly Research Payment is less than the Advance Research Payment Amount, Isis shall promptly make a payment to the Foundation in an amount equal to the amount by which the Advance Research Payment Amount exceeded the amount of the final Quarterly Research Payment.

(ii) **Payment Remittance.** Subject to the terms and conditions of this Agreement, each payment to be made by the Foundation under this Agreement will be due and payable by the Foundation within [***] of the date of the receipt by the Foundation of the invoice issued by Isis in accordance with this Agreement in respect of such payment. All payments made by the Foundation under this Agreement will be paid by check in US Dollars and remitted to Isis at the address set forth in Section 19 of this Agreement. Any payment made by the Foundation under this Agreement in respect of an invoice issued by Isis under this Agreement using a currency other than US Dollars will be converted by the Foundation to US Dollars at the exchange rate prevailing on or about the date that the Foundation remits such payment to Isis.

Project Results

7. **Ownership of Project Results; Notification and Delivery of Project Results; Withdrawal of Project Results; Transfers of the Project Results to Collaborators.**

(a) **Ownership of Project Results.** Isis and the Foundation will own [***] all Project Results. The ownership of the Project Results will vest in the Parties in that manner immediately upon creation. Each Party hereby assigns, and agrees to assign, to the other Party sufficient right, title and interest in the Project Results to accomplish such ownership. Each of Isis and the Foundation agrees that it will not sell or otherwise transfer (including by sale of assets or stock or by merger or other business combination) its title to any Project Results to any Third Party or Affiliate unless such Third Party or Affiliate takes title to such Project Results (i) subject to the rights of the non-transferring Party in such Project Results under this Agreement and (ii) assumes the obligations of the transferring Party with respect to such Project Results under this Agreement; *provided, however*, that the transferring Party will (A) notify the non-transferring Party in writing within 10 days after any such transfer and (B) provide the non-transferring Party with a copy of the written assignment and assumption or similar agreement between the transferring Party and the Third Party or Affiliate transferee.

(b) **Notification and Delivery of Project Results; Withdrawal of Project Results.**

(i) **Notification and Delivery of Project Results.**

(A) **General.** Isis will inform the Foundation of, and deliver, the Project Results to the Foundation within a reasonable period of time following the conception, discovery, invention or production, as the case may be, of each such Project Result through the Steering Committee meetings, Project Reports and the transmittal of the raw data underlying the Project Results pursuant to Section 5(f) of this Agreement.

(B) **Delivery of Additional Project Activities Project Results.** Isis has informed the Foundation of, and delivered, the Project Results relating to the programs of Research performed by, or on behalf of, Isis as described in the Additional Project Activities Description to the Foundation in a series of reports (collectively, the "***Additional Project Activities Project Results***"). Within [***] of the Effective Date, the Additional Project Activities Project Results previously delivered to the Foundation will be compiled by Isis and organized into a master report and redelivered to the Foundation (the "***Additional Project Activities Project Results Report***"), and will include an activity index listing each slide/page of such report relevant to each particular activity.

(ii) **Withdrawal of Project Results.** If at any time after informing the Foundation of the Project Results pursuant to Section 7(b)(i) of this Agreement Isis determines that there is a reasonable scientific basis to conclude that all or a portion of such Project Results are not scientifically valid or accurate, Isis will promptly so notify the Foundation in writing.

(c) **Transfers of the Project Results to Collaborators; Uses of Project Results.**

(i) **Transfers of the Project Results by Isis to Third Party Collaborators; Uses of Project Results.** Isis may transfer or have transferred the Project Results to any of its Affiliates or one or more Third Party collaborators; *provided, that*, any such Affiliate or Third Party collaborator has entered into an agreement with Isis which requires such Affiliate or Third Party collaborator to maintain similar, but no less burdensome, obligations of confidentiality and non-use set forth in Section 14(c) of this Agreement. Subject to the foregoing, Isis and each of its Affiliates and Third Party collaborators shall only have the right to use the Project Results for all uses and purposes permitted under this Agreement.

(ii) **Transfers of the Project Results by the Foundation to Foundation Collaborators; Uses of Project Results.** The Foundation may transfer or have transferred the Project Results to any of its Affiliates or one or more Foundation Collaborators; *provided, that*, any such Affiliate or Foundation Collaborator has entered into an agreement with the Foundation which requires such Affiliate or Foundation Collaborator to maintain similar, but no less burdensome, obligations of confidentiality and non-use set forth in Section 14(c) of this Agreement. Subject to the foregoing, the Foundation and each of its Affiliates and Foundation Collaborators shall only have the right to (A) use the Project Results for all uses and purposes relating to HD Research and Development and (B) exercise the license rights granted by Isis pursuant to Section 10 and Section 12 of this Agreement.

Project Deliverables; Requests for Project Compounds

8. **Ownership of Project Deliverables; Delivery of Project Deliverables; Transfers of the Project Deliverables to Foundation Collaborators; Grant of HD Field of Use License to Isis; Isis' Option to Negotiate Additional License Rights Outside the HD Field of Use; Transfers of the Project Deliverables to Foundation Collaborators; Requests for Project Compounds; Approval of Foundation Project Compound Requests; Criteria for Approving Foundation Project Compound Requests; Basis for Determination to not Approve a Foundation Project Compound Request; Delivery of Approved Foundation Requested Project Compounds; Use of Approved Foundation Requested Project Compounds; Payment for Approved Foundation Requested Project Compounds; Invoicing; Payment Remittance; Delivery and Use of Results Arising from the use of the Project Deliverables.**

(a) **Ownership of Project Deliverables.** Notwithstanding any provision of this Agreement to the contrary, as between the Foundation and Isis, the Foundation will solely own all Project Deliverables. Isis hereby assigns, and agrees to assign, to the Foundation any and all right, title and interest of Isis in and to the Project Deliverables. The ownership of each Project Deliverable will vest in the Foundation immediately upon production of such Project Deliverable. Upon the written request of the Foundation, Isis will execute such documents and do all other acts and things as may be reasonably deemed necessary by the Foundation to effectuate and assure that all right, title and interest of Isis in and to each Project Deliverable vest in the Foundation (or its designee). The Foundation will reimburse Isis for all reasonable out-of-pocket costs and expenses actually incurred by Isis to execute and deliver to the Foundation any such document(s) referred to immediately above. For the avoidance of any doubt, notwithstanding any provision of this Agreement to the contrary, the ownership of a Project Deliverable by the Foundation does not grant any ownership rights to the Foundation in any Intellectual Property embodied in or related to such Project Deliverable as the ownership of any such Intellectual Property is governed solely by the terms of Section 9 of this Agreement.

(b) **Delivery of Project Deliverables; Transfers of the Project Deliverables to Foundation Collaborators; Grant of HD Field of Use License to Isis; Isis' Option to Negotiate Additional License Rights Outside the HD Field of Use.**

(i) **Delivery of Project Deliverables.** Promptly following the production of each Project Deliverable, Isis will deliver such Project Deliverable to the Foundation. All Project Deliverables will be shipped to the delivery point specified by the Foundation in writing to Isis.

(ii) **Transfers of the Project Deliverables to Foundation Collaborators; Grant of HD Field of Use License to Isis; Isis' Option to Negotiate Additional License Rights Outside the HD Field of Use.**

(A) **Transfers of the Project Deliverables to Foundation Collaborators.** The Foundation may transfer or have transferred the Project Deliverables to one or more Foundation Collaborators; *provided, that*, any such Foundation Collaborator has entered into an agreement with the Foundation which requires such Foundation Collaborator to maintain similar, but no

less burdensome, obligations of confidentiality and non-use set forth in Section 14(c) of this Agreement. The Foundation and the Foundation Collaborators shall have the right to (A) use the Project Deliverables for all uses and purposes relating to HD Research and Development and (B) exercise the license rights granted by Isis pursuant to Section 10 and Section 12 of this Agreement

(B) **Grant of HD Field of Use License to Isis.** The Foundation hereby grants (and will require the Foundation Collaborators that use any Project Deliverables to grant) Isis a fully paid-up, royalty-free, irrevocable, perpetual, worldwide, non-exclusive license solely in the HD Field of Use under any Intellectual Property that claims a method of using a Project Compound conceived, discovered, invented, made or first reduced to practice in the course of the Foundation's or a Foundation Collaborator's use of the Project Deliverables.

(C) **Isis' Option to Negotiate Additional License Rights Outside the HD Field of Use.** In addition to the non-exclusive license referred to in Section 8(b)(ii)(B) of this Agreement, the Foundation grants to Isis an exclusive option (each, a "***Project Deliverable Option***") to acquire a worldwide license under any Intellectual Property that claims a method of using a Project Compound conceived, discovered, invented, made or first reduced to practice in the course of the Foundation's or a Foundation Collaborator's use of the Project Deliverables for uses *outside of* the HD Field of Use, which option will extend for a period (each, a "***Project Deliverable Option Exercise Period***") of three (3) months following receipt of a notice from the Foundation disclosing any such Intellectual Property (which notice may be satisfied by the Foundation's delivery of the written reports described in Section 8(d) of this Agreement). With respect to any such Intellectual Property that is subject to a Project Deliverable Option, Isis shall exercise such Project Deliverable Option by providing written notice to the Foundation prior to the expiration of the Project Deliverable Option Exercise Period in respect of such Project Deliverable Option. If Isis exercises a Project Deliverable Option, then Isis shall have a period (each, a "***Project Deliverables License Negotiation Period***") of one hundred and twenty (120) days following the delivery by Isis of the Project Deliverable Option Exercise Notice in respect of such Project Deliverable Option within which to negotiate and execute a license in respect of the Intellectual Property subject to such Project Deliverable Option. Each of the Foundation and Isis agree (1) to negotiate any such license in good faith and (2) that, upon the mutual agreement of the Foundation and Isis, to extend the Project Deliverable License Negotiation Period in respect of such license for an additional period(s) not to exceed an additional one hundred and twenty (120) days, in the aggregate.

(c) **Requests for Project Compounds; Approval of Foundation Project Compound Requests; Criteria for Approving Foundation Project Compound Requests; Basis for Determination to not Approve a Foundation Project Compound Request; Delivery of Approved Foundation Requested Project Compounds; Use of Approved Foundation Requested Project Compounds; Grant of HD Field of Use License to Isis; Isis' Option to Negotiate Additional License Rights Outside the HD Field of Use; Payment for Approved Foundation Requested Project Compounds; Invoicing; Payment Remittance.**

(i) **Requests for Project Compounds.** At any time, and from time to time, during the period beginning on [***] and ending on the date that is [***] following the expiration or termination of the Term (the "***Foundation Project Compound Request Period***"), the Foundation may request that Isis provide the Foundation with one or more Project Compounds for use by the Foundation to conduct defined research activities by providing a written notice (the "***Foundation Project Compound Request Notice***") to Isis (A) identifying each Project Compound (each such Project Compound, a "***Foundation Requested Project Compound***") and the requested amount thereof (with a minimum requested amount per Foundation Requested Project Compound of [***]) and (B) a reasonably detailed description of the proposed research activities (each such program of proposed research activities, a "***Foundation Project Compound Study***") to be conducted using each Foundation Requested Project Compound.

(ii) **Approval of Foundation Project Compound Requests; Criteria for Approving Foundation Project Compound Requests; Basis for Determination to not Approve a Foundation Project Compound Request.**

(A) **Approval of Foundation Project Compound Requests.** Within [***] of the receipt by Isis of a Foundation Project Compound Request Notice, Isis will make a determination regarding the Foundation's request for the use of the Foundation Requested Project Compounds for the Foundation Requested Project Compound Studies specified in such Foundation Project Compound Request Notice. As part of Isis' consideration of any such request, Isis may request that the Parties convene a Steering Committee meeting (or, after the Term, convene representatives of each Party) to facilitate its consideration of any such request. With respect to any decision regarding the approval of any request by the Foundation to use Foundation Requested Project Compounds for the Foundation Requested Project Compound Studies, Isis will (1) act in good faith and on a responsive basis and (2) make such decision on a reasonable basis using the criteria set forth in this Section 8(c)(ii). Each Foundation Requested Project Compound and each Foundation Project Compound Study that is approved by

Isis in accordance with this Section 8(c)(ii) will, for all purposes of this Agreement, be referred to as an "***Approved Foundation Requested Project Compound***" and "***Approved Foundation Project Compound Study***", respectively.

(B) **Criteria for Approving Foundation Project Compound Requests.** Isis will approve each request by the Foundation to use a Foundation Requested Project Compound for a Foundation Project Compound Study unless any of the following are

determined by Isis to be true:

[***]

(C) **Basis for Determination to not Approve a Foundation Project Compound Request.** If Isis does not approve a request by the Foundation to use a Foundation Requested Project Compound for a Foundation Project Compound Study, Isis will, no later than [***] of the receipt by Isis of a Foundation Project Compound Request Notice for such request, deliver to the Foundation a written notice setting forth in reasonable detail Isis' basis under the criteria set forth in Section 8(c)(ii)(B) of this Agreement for not approving such request. Isis agrees that, if Isis does not approve such a request, the Foundation may dispute such determination by Isis and seek resolution pursuant to Section 5(a)(iii)(B) of this Agreement.

(iii) **Delivery of Approved Foundation Requested Project Compounds.** Following Isis' approval of a request by the Foundation to use a Foundation Requested Project Compound for a Foundation Project Compound Study, Isis will use reasonable commercial efforts to (A) manufacture such Approved Foundation Requested Project Compound in accordance with the standards and specifications developed for such Approved Foundation Requested Project Compound during the course of the conduct of the Project and (B) supply the Foundation with the amount of such Approved Foundation Requested Project Compound within a reasonable period of time following such approval.

(iv) **Use of Approved Foundation Requested Project Compounds; Grant of HD Field of Use License to Isis; Isis' Option to Negotiate Additional License Rights Outside the HD Field of Use.**

(A) **Use of Approved Foundation Requested Project Compounds.** The Foundation agrees that each Approved Foundation Requested Project Compound will be used by the Foundation and the Foundation Collaborators for the sole purpose of conducting the Approved Foundation Project Compound Study for which such Approved Foundation Requested Project Compound was approved.

(B) **Grant of HD Field of Use License to Isis.** The Foundation hereby grants (and will require the Foundation Collaborators that use any Approved Foundation Requested Project Compound to grant) Isis a fully paid-up, royalty-free, irrevocable, perpetual, worldwide, non-exclusive license solely in the HD Field of Use under any Intellectual Property that claims a method of using an Approved Foundation Requested Project Compound conceived, discovered, invented, made or first reduced to practice in the course of the Foundation's or a Foundation Collaborator's use of an Approved Foundation Requested Project Compound.

(C) **Isis' Option to Negotiate Additional License Rights Outside the HD Field of Use.** In addition to the non-exclusive license referred to in Section 8(c)(iv)(B) of this Agreement, the Foundation grants to Isis an exclusive option (each, an "***Approved Foundation Requested Project Compound Option***") to acquire a worldwide license under any Intellectual Property that claims a method of using an Approved Foundation Requested Project Compound conceived, discovered, invented, made or first reduced to practice in the course of the Foundation's or a Foundation Collaborator's use of the Approved Foundation Requested Project Compound for uses *outside of* the HD Field of Use, which option will extend for a period (each, an "***Approved Foundation Requested Project Compound Option Exercise Period***") of three (3) months following receipt of a notice from the Foundation disclosing any such Intellectual Property (which notice may be satisfied by the Foundation's delivery of the written reports described in Section 8(d) of this Agreement). With respect to any such Intellectual Property that is subject to an Approved Foundation Requested Project Compound Option, Isis shall exercise such Approved Foundation Requested Project Compound Option by providing written notice to the Foundation prior to the expiration of the Approved Foundation Requested Project Compound Option Exercise Period in respect of such Approved Foundation Requested Project Compound Option. If Isis exercises an Approved Foundation Requested Project Compound Option, then Isis shall have a period (each, an "***Approved Foundation Requested Project Compound License Negotiation Period***") of one hundred and twenty (120) days following the delivery by Isis of the Approved Foundation Requested Project Compound Option Exercise Notice in respect of such Approved Foundation Requested Project Compound Option within which to negotiate

and execute a license in respect of the Intellectual Property subject to such Approved Foundation Requested Project Compound Option. Each of the Foundation and Isis agree (1) to negotiate any such license in good faith and (2) that, upon the mutual agreement of the Foundation and Isis, to extend the Approved Foundation Requested Project Compound License Negotiation Period in respect of such license for an additional period(s) not to exceed an additional one hundred and twenty (120) days, in the aggregate.

(v) **Payment for Approved Foundation Requested Project Compounds; Invoicing; Payment Remittance.** The Foundation will pay Isis a fee of US$[***] per [***] (or portion thereof) per Approved Foundation Requested Project Compound delivered to the Foundation pursuant to, and in accordance with, this Section 8(c). Simultaneously with the delivery of each Approved Foundation Requested Project Compound, Isis will deliver to the Foundation an invoice for payment in respect of such Approved Foundation Requested Project Compound. Each invoice delivered by Isis for an Approved Foundation Requested Project Compound will (A) reference the "RecID" number set forth in the footer of this Agreement, (B) be issued in US Dollars and (C) be itemized and contain detailed information in respect of the Approved Foundation Requested Project Compound being billed for under such invoice. Subject to the terms and conditions of this Agreement, each payment to be made by the Foundation in respect of an Approved Foundation Requested Project Compound under this Agreement will be due and payable by the Foundation within 60 days of the date of the receipt by the Foundation of the invoice issued by Isis in accordance with this Agreement in respect of such payment. All such payments made by the Foundation under this Agreement will be paid by check in US Dollars and remitted to

Isis at the address set forth in Section 19 of this Agreement. For the avoidance of doubt, unless otherwise approved by the Steering Committee pursuant to Section 13(a)(ii)(E) of this Agreement, the (1) cost of any Approved Foundation Requested Project Compound Studies conducted by the Foundation or the Foundation Collaborators and (2) amounts paid to Isis under this Section 8(c)(v) for Approved Foundation Requested Project Compounds, will not be reimbursed by Isis under this Agreement, and will not be considered "*Revenue*" under Section 13 of this Agreement.

(d) **Delivery and Use of Results Arising from the use of the Project Deliverables.** The Foundation will deliver to Isis a written report setting forth a summary of all data, formulae, methods, outcomes, protocols or other results produced by the Foundation or any Foundation Collaborator using the Project Deliverables (including any Approved Foundation Requested Project Compound). Each such report (A) will be delivered to Isis within a reasonable period of time following the completion of the research activities in which the Project Deliverables were

used, (B) will be in substantially the same format and contain the same degree of detail as the Foundation generally uses to communicate such information internally and to its Third Party research collaborators and (C) will include a copy of (1) each report related such results received by the Foundation from a Third Party or Affiliate and (2) all final versions of written documents created by the Foundation summarizing such results and not otherwise included in the any of the reports described in (1) above that are delivered to Isis. Isis agrees that all reports and results delivered by the Foundation to Isis pursuant to this Section 8(d) shall be deemed the Confidential Information of the Foundation and, notwithstanding any other provision of this Agreement, may only be (a) used by Isis for Research and Development, (b) disclosed in accordance with, and to only those Third Parties and Affiliates expressly permitted by, Section 14(c) of this Agreement, and (c) licensed by Isis to a Third Party under a Commercial License (subject to such Third Party's agreement to keep such reports and results confidential under terms no less restrictive as those set forth in Section 14 of this Agreement). Isis acknowledges and agrees that, notwithstanding the foregoing, except as otherwise provided in this Section 8(d) or Section 8(b)(ii) or Section 8(c)(iv) of this Agreement, no license or other rights are granted to Isis with respect to any Intellectual Property covering or claiming, or otherwise embodied in, such reports or the information contained therein.

Intellectual Property

9. **Ownership of Background Intellectual Property; Ownership of Project Intellectual Property; Grant of Exclusive License to the Project HD Intellectual Property by the Foundation Outside the HD Field of Use; Disclosure of Inventions; Inventorship; Prosecution of Patentable Project HD Intellectual Property; Disclaimer of Interest in Patentable Project Intellectual Property; Infringement or Misappropriation of Project Intellectual Property.**

(a) **Ownership of Background Intellectual Property.**

(i) **Ownership of Isis Background Intellectual Property.** As between the Foundation and Isis, Isis will solely own all Isis Background Intellectual Property. Except as expressly set forth in this Agreement, the Foundation will have no ownership or other interest in any Isis Background Intellectual Property.

(ii) **Ownership of Foundation Background Intellectual Property.** As between the Foundation and Isis, the Foundation will solely own all Foundation Background Intellectual Property. Except as expressly set forth in this Agreement, Isis will have no ownership or other interest in any Foundation Background Intellectual Property.

(b) **Ownership of Project Intellectual Property; Grant of Exclusive License to the Project HD Intellectual Property by the Foundation Outside the HD Field of Use.**

(i) **Ownership of Project Intellectual Property.**

(A) **Ownership of Project Non-HD Intellectual Property.** As between the Foundation and Isis, Isis will solely own all Project Non-HD Intellectual Property. Except as expressly set forth in this Agreement, the Foundation will have no ownership or other interest in any Project Non-HD Intellectual Property.

(B) **Ownership of Project HD Intellectual Property.** Isis and the Foundation will own [***] all Project HD Intellectual Property. The ownership of the Project HD Intellectual Property will vest in the Parties in that manner immediately upon creation. Each Party hereby assigns to the other Party sufficient right, title and interest in the Project HD Intellectual Property to accomplish such ownership. Neither Isis nor the Foundation will sell or otherwise transfer (including by sale of assets or stock or by merger or other business combination) its title to any Project HD Intellectual Property (including any Reverted Project HD Intellectual Property (as defined in Section 9(b)(iii)(A) of this Agreement)) to any Third Party or Affiliate unless such Third Party or Affiliate takes title to such Project HD Intellectual Property (1) subject to the rights of the non-transferring Party in such Project HD Intellectual Property under this Agreement and (2) assumes in writing the obligations of the transferring Party with respect to such Project HD Intellectual Property under this Agreement, including the limitations under this Agreement relating to the transferring Party's use of such Project HD Intellectual Property; *provided*, *however*, that the transferring Party will a) notify the non-transferring Party in writing within 10 days after any such transfer and b) provide the non-transferring Party with a copy of the relevant part of the written assignment and assumption or similar agreement between the transferring Party and the Third Party or Affiliate transferee.

(ii) **Grant of Exclusive License to the Project HD Intellectual Property by the Foundation Outside the HD Field of Use.** The Foundation grants to Isis a fully paid-up, royalty-free, worldwide exclusive license under any Project HD Intellectual Property (including (A) any patent application, divisional, continuation, continuation-in-part, substitute, renewal, reexamination, extension

or reissue in respect of any applicable patent or (B) any intellectual property rights claimed in respect of any applicable patent), to use the Project HD Intellectual Property for any use or purpose outside the HD Field of Use. The license rights granted by the Foundation

under this Section 9(b)(ii) will be subject to termination by the Foundation in the event of Isis' material breach of this Agreement if such material breach is not cured within 45 days following receipt by Isis of notice of such material breach.

(iii) **Reversion of Foundation's Rights in Project HD Intellectual Property.**

(A) **Reversion of Foundation's Rights in Project HD Intellectual Property.** Upon the termination of this Agreement by the Foundation pursuant to Section 17(b)(i) of this Agreement, subject to (1) the rights reserved by the Foundation pursuant to Section 9(b)(iii)(B) of this Agreement and (2) the Foundation's Revenue (as defined in Section 13(a) of this Agreement) sharing rights set forth in Section 13 of this Agreement, all of the Foundation's right, title and interest in and to the Project HD Intellectual Property will revert to Isis (after such termination, all Project HD Intellectual Property shall also be referred to herein as "***Reverted Project HD Intellectual Property***").

(B) **The Foundation's Right to Use Reverted Project HD Intellectual Property.** With respect to all Reverted Project HD Intellectual Property, the Foundation hereby reserves, and Isis hereby grants to the Foundation, a fully paid-up, royalty-free, irrevocable, perpetual, world-wide non-exclusive license (including a license under any related Intellectual Property rights) for all uses and purposes related to HD Research and Development including to (1) make, have made, use and have used products or processes resulting from such Reverted Project HD Intellectual Property, (2) practice and have practiced such Reverted Project HD Intellectual Property and (3) use and have used the Confidential Information relating to such Reverted Project HD Intellectual Property; *provided*, *however*, that, the foregoing license (1) will be for HD Research and Development only, (2) will not include any right to manufacture or distribute for sale or sell, (3) will not be subject to royalties or other fees and (4) will include the right to grant sublicenses on the same terms; *provided*, *further that*, such sublicense (i) is granted without payment of royalties, other fees or profit and (ii) prohibits the sublicensee from granting sublicenses.

(c) **Disclosure of Inventions; Inventorship.**

(i) **Disclosure of Inventions.** If either Party believes that any Intellectual Property has been conceived, discovered, invented, made or first reduced to practice in the course of the performance of the Research, such Party will promptly give notice (each, an "***Invention Notice***") of such Intellectual Property to the other Party.

(ii) **Inventorship.** The identity of the inventor(s) of all patentable Intellectual Property that has been conceived, discovered, invented, made or first reduced to practice in the course of the performance of the Research will be determined in accordance with United States Patent law (or, if the jurisdiction in which patent or other protection is being sought does not permit the application of United States Patent law to identify the inventor, then in accordance with the applicable law in that jurisdiction).

(d) **Prosecution of Patentable Project HD Intellectual Property.**

(i) **Responsibility for Prosecution of Patentable Project HD Intellectual Property.** Isis will prepare, file, prosecute and maintain the appropriate filings in respect of any Patentable Project HD Intellectual Property including filing (A) a provisional patent application or (B) a patent application (including a patent application corresponding to a previously filed provisional patent application) claiming any such Patentable Project HD Intellectual Property in the United States and in such other jurisdictions as the Steering Committee jointly determine in good faith are necessary in order to protect Isis' and the Foundation's rights in such Patentable Project HD Intellectual Property. Isis will ensure that all such filings are filed in the name of Isis and the Foundation as co-owners.

(ii) **Foundation Election to have Prosecution of Patentable Project HD Intellectual Property Initiated.** At any time and from time to time, the Foundation will have the right to elect to cause Isis to prepare, file, prosecute and maintain the appropriate filings in respect of any Patentable Project HD Intellectual Property which is the subject of an Invention Notice by providing notice (a "***Foundation Patent Filing Election Notice***") of such election to Isis. Promptly following the receipt of a Foundation Patent Filing Election Notice, Isis will, to the extent not prohibited by any Commercial License then in effect, prepare, file, prosecute and maintain the appropriate filings in respect of the Patentable Project Intellectual Property which is the subject of a Foundation Patent Filing Election Notice, including filing (A) a provisional patent application or (B) a patent application (including a patent application corresponding to a previously filed provisional patent application) claiming any such Patentable Project Intellectual Property in the United States and in such other jurisdictions as the Steering Committee jointly determine in good faith are necessary in order to protect Isis' and the Foundation's rights in such Patentable Project HD Intellectual Property. Isis will ensure that all such filings are filed in the name of Isis and the Foundation as co-owners.

(iii) **Covenants of Isis.** With respect to the prosecution and maintenance by Isis of any Patentable Project HD Intellectual Property pursuant to this Section 9(d), Isis will use commercially reasonable efforts to promptly (A)

give all notices required by, and comply with all other requirements of, applicable law to reasonably preserve the Parties' rights in such Patentable Project HD Intellectual Property as appropriate; (B) prepare, file, prosecute and maintain, as applicable, the appropriate filings and patents to reasonably protect the Parties' rights in such Patentable Project HD Intellectual Property; (C) provide the Foundation with a copy of any proposed filings in respect of such Patentable Project HD Intellectual Property at least 15 days prior to the filing of such proposed filings; (D) provide the Foundation with a copy of any provisional patent application or patent application filed claiming such Patentable Project HD Intellectual Property; (E) provide the Foundation with copies of all correspondence and other documents relating to the prosecution and maintenance of such Patentable Project HD Intellectual Property that come into the possession or control of Isis; and (F) such other documents and information related to such Patentable Project HD Intellectual Property as the Foundation may reasonably request and Isis can provide without incurring unreasonable cost and expense.

(iv) **Patent Expenses.** Each Party will be responsible for 100% of the Patent Expenses incurred by such Party.

(e) **Disclaimer of Interest in Patentable Project HD Intellectual Property.**

(i) **Disclaimer Notice.** With respect to any Patentable Project HD Intellectual Property, either Party may, at any time, disclaim its interest in such Patentable Project HD Intellectual Property by providing notice of such election ("***Patentable Project HD Intellectual Property Disclaimer Notice***") to the other Party. Isis will be deemed to have disclaimed its interest in any Patentable Project HD Intellectual Property that is the subject of a Foundation Patent Filing Election Notice if Isis fails to comply with the obligations set forth in Section 9(d) of this Agreement with respect to such Patentable Project HD Intellectual Property within 45 days of Isis' receipt of the Patentable Project HD Intellectual Property Disclaimer Notice in respect of such Patentable Project HD Intellectual Property.

(ii) **Effect of Disclaimer Notice.** In the event that a Patentable Project HD Intellectual Property Disclaimer Notice is delivered by either Party in respect of Patentable Project HD Intellectual Property: (A) the disclaiming Party hereby assigns its ownership interest in such Patentable Project HD Intellectual Property to the non-disclaiming Party without consideration, and will execute all documents reasonably necessary to perfect such assignment at the non-disclaiming Party's cost; (B) except as expressly set forth in this Agreement, the disclaiming Party will have no further rights to such Patentable Project HD Intellectual Property; and (C) the disclaiming Party will, at any time during and after the term of this

Agreement, cooperate with the non-disclaiming Party without consideration but at the expense of the non-disclaiming Party in preparing, filing, prosecuting and maintaining, as applicable, the appropriate filings to protect the non-disclaiming Party's rights in such Patentable Project HD Intellectual Property, including obtaining execution by its employees of any documents necessary in connection with such activities. Each of the Parties will use reasonable efforts to keep the other Party advised of its deliberations regarding its determinations as to electing to disclaim its interest in any Patentable Project HD Intellectual Property.

(f) **Infringement or Misappropriation of Project Intellectual Property.**

(i) **Infringement or Misappropriation of Project Intellectual Property by Third Parties.** Each Party will promptly notify each other in writing of any alleged or threatened infringement or misappropriation of any Project Intellectual Property of which it becomes aware. In connection with any such alleged or threatened infringement or misappropriation, each Party will confer and take such action and allocate recoveries in such manner as they in good faith may mutually agree. Neither Isis nor the Foundation will settle a claim brought against a Third Party in respect of such infringement or misappropriation without the consent of the other Party, which consent will not be unreasonably withheld, delayed or conditioned.

(ii) **Infringement or Misappropriation Claims by Third Parties Related to Project Intellectual Property.** Each Party will promptly notify the other Party in writing if any Third Party alleges that the use or practice of any Project Intellectual Property infringes or misappropriate such Third Party's Intellectual Property rights. In connection with any such alleged infringement or misappropriation, each Party will confer and take such action in such manner as they in good faith may mutually agree. Neither Party will settle a claim brought by a Third Party in respect of such infringement or misappropriation without the consent of the other Party, which consent will not be unreasonably withheld, delayed or conditioned.

(iii) **Infringement or Misappropriation Outside of the HD Field of Use.** Notwithstanding the foregoing in this Section 9(f), Isis has the sole right (but not the obligation) to assume direction and control of the prosecution and/or defense of any claim against or alleged by a Third Party outside of the HD Field of Use that involves actual or potential infringement or misappropriation of any Project Intellectual Property, or alleges that the use or practice of any Project Intellectual Property infringes or misappropriates a Third Party's Intellectual Property rights (Isis' right shall include the sole right to settle such a claim in Isis' sole discretion, *provided that* such settlement does not (A) admit any fault or negligence on the part of the Foundation and/or its Affiliates, (B) impose any obligation on the Foundation and/or its Affiliates or (C) without the prior

written consent of the Foundation (which consent shall not unreasonably withheld, conditioned or delayed), adversely affect the Foundation and/or its Affiliates in any way.

10. **Licenses to Project HD Intellectual Property and Project Compounds in the HD Field of Use.**

(a) **Commercialization of Project HD Intellectual Property and Project Compounds; Reservation of Rights Regarding Project HD Intellectual Property and Project Compounds.**

(i) **Commercialization of Project HD Intellectual Property and Project Compounds.** Except as expressly permitted by this Agreement, neither Party will use or otherwise exploit any Project HD Intellectual Property or any Project Compound for any use or purpose or grant any license of any Project HD Intellectual Property or any Project Compound for any use or purpose. Except as expressly permitted by Section 10(a)(ii) of this Agreement, (1) the use or other exploitation of any Project HD Intellectual Property or any Project Compound by either of the Parties, an Affiliate of either Party or a Third Party and (2) the grant of any license of any Project HD Intellectual Property or any Project Compound by either of the Parties to an Affiliate of either Party or a Third Party, in each case for uses other than Research and Development in the HD Field of Use, will only be done pursuant to the grant of a commercial license under a license agreement executed by both Parties (any such license will hereinafter be referred to as a "***Commercial License***"). For the avoidance of any doubt, the Parties agree that this Section 10 shall not apply to a) the use or other exploitation or b) the grant of any license for any purpose of any Project HD Intellectual Property or any Project Compound outside the HD Field of Use.

(ii) **Reservation of Rights by the Parties to Grant Certain Licenses.**

(A) **Isis' Right to Use Project Intellectual Property and Project Compounds.** Isis reserves the right to use any Project HD Intellectual Property and any Project Compound for all uses and purposes relating to Research and Development.

(B) **Isis' Right to Grant Research and Development Licenses.** Isis reserves the right to grant non-exclusive licenses throughout the world in respect of any Project HD Intellectual Property or any Project Compound for all uses and purposes relating to Research and Development.

(C) **Foundation's Right to Use Project HD Intellectual Property and Project Compounds.** The Foundation reserves the right to use

any Project HD Intellectual Property and any Project Compound for all uses and purposes relating to HD Research and Development.

(D) **Foundation's Right to Grant HD Research and Development Licenses.** The Foundation reserves the right to grant non-exclusive licenses throughout the world in respect of any Project HD Intellectual Property or any Project Compound for all uses and purposes relating to HD Research and Development.

(b) **Conduct of Human Clinical Trials.**

(i) **Obligation to the Parties to Confer.** Isis and the Foundation will confer with each other on the conduct of human clinical trials involving any Project Compound prior to the initiation of any human clinical trials for such Project Compound.

(ii) **Isis' Right to Conduct Human Clinical Trials.** Subject to Section 10(b)(i) of this Agreement, but notwithstanding any other provision of this Agreement, Isis will have the right to conduct human clinical trials involving any Project Compound.

(iii) **Foundation's Right to Conduct Human Clinical Trials.** Subject to Section 10(b)(i) of this Agreement, if (A) within [***] of Isis' receipt of a request from the Foundation for Isis to undertake the conduct of a human clinical trial involving a Project Compound reasonably required to advance such Project Compound for the diagnosis, treatment, cure or prevention of Huntington's disease, Isis does not agree to promptly initiate and conduct such a human clinical trial or (B) the Parties decide that the Foundation will conduct human clinical trials concurrently with a human clinical trial being conducted by Isis, the Foundation will have the right to conduct human clinical trials on its own or through or with a Third Party selected by the Foundation. For the avoidance of doubt, the Foundation will have the right to use Isis Background Intellectual Property, Project HD Intellectual Property and Project Compounds for the conduct of any such human clinical trials.

(c) **Right to Make Proposal Regarding the Granting of a Commercial License.**

(i) The Parties agree (1) that either Party may submit to the Parties for their consideration under this Section 10 a proposal for the granting of a Commercial License and (2) to consult and make a determination regarding the granting of a Commercial License in respect of such proposal in accordance with the provisions of this Section 10.

(ii) If (1) the Parties are evaluating multiple proposals (including one submitted by Isis or an Affiliate of Isis pursuant to which Isis or an Affiliate of Isis would be granted a Commercial License (the "***Isis Proposal***")) to determine whether or not the principles and guidelines set forth in this Section 10 for the granting of a Commercial License have been satisfied and (2) more than one of such proposals (including an Isis Proposal) satisfies the principles and guidelines set forth in this Section 10 on a substantially equivalent basis, the Foundation agrees to accept the Isis Proposal and agrees to grant a Commercial License to Isis in accordance with this Section 10.

(d) **Principles and Guidelines for Granting Commercial Licenses.**

(i) **Good Faith Consultations.** The Parties will consult, and work in a collaborative fashion, with each other in accordance with the provisions of this Section 10 concerning the grant of any Commercial License. With respect to any decision regarding the granting of any Commercial License, the Parties will (A) act in good faith and on a responsive basis and (B) make such decision on a reasonable basis using the principles and guidelines set forth in this Section 10(d). In addition, neither Isis nor the Foundation will

unreasonably withhold, delay or condition their consent to a Commercial License or demand additional payments beyond those required under this Agreement.

(ii) **Fundamental Principles and Guidelines.** A Commercial License will be granted if and only if the Parties mutually agree that the granting of such Commercial License is reasonably likely to:

(A) maximize the impact on the health and well-being of Huntington's disease patients;

(B) maximize the availability of diagnostic or therapeutic products to Huntington's disease patients; and

(C) maximize the speed of which diagnostic or therapeutic products are available to Huntington's disease patients.

(iii) **Availability of Products as Primary Factor for Granting Commercial Licenses.** Subject to Section 10(d)(iv), if (A) the Parties are evaluating multiple proposals (including an Isis Proposal) for the granting of a Commercial License, (B) more than one of the proposals satisfies the principles and guidelines set forth in this Section 10 (other than (1) the proposed economic terms and (2) the proposed time frame for making the diagnostic or therapeutic product which is to be the subject of such Commercial License available to Huntington's disease patients) on a substantially equivalent basis; and (C) one of the proposals sets forth a

time frame for making the diagnostic or therapeutic product which is to be the subject of such Commercial License available to Huntington's disease patients that is substantially shorter than those set forth in the other proposals being considered by the Parties, then the proposal setting forth such substantially shorter time frame, if accompanied by firm diligence obligations, will be accepted by the Parties and a Commercial License granted to the entity making such proposal even if the economic terms of such proposal are substantially less than those set forth in the other proposals being considered by the Parties.

(iv) **Commercial License Agreement Terms and Conditions.** In addition to the principles and guidelines set forth in Section 10(d)(ii) and Section 10(d)(iii) of this Agreement, a Commercial License will be granted if and only if the Parties mutually agree that the terms and conditions of the license agreement in respect of such Commercial License incorporates the following terms, principles and guidelines:

(A) reasonable performance milestones and a demonstrated capacity of the licensee to be able to meet those milestones; and

(B) reasonable business and other terms and conditions that are in keeping with the then existing market standards for agreements of such type and nature in respect of similar technology and in similar disease indications.

(e) **Resolution of Disputes Regarding the Granting of Commercial Licenses.** If the Parties cannot reach a mutual agreement regarding the granting of a Commercial License in respect of a proposal for the granting of a Commercial License submitted by either of the Parties for their consideration in accordance with the provisions of this Section 10 (each, a "***Commercial License Grant Dispute***"), either Party may submit such Commercial License Grant Dispute to B. Lynne Parshall, in the case of Isis (or such other individual identified in writing by Isis), and Robi Blumenstein, in the case of the Foundation (or such other individual identified in writing by the Foundation), for resolution by providing a written notice (each, a "***Internal Commercial License Grant Dispute Resolution Notice***") to the other Party setting forth in reasonable detail the basis of such Commercial License Grant Dispute. Such individuals will, within 20 days after such Internal Commercial License Grant Dispute Resolution Notice is delivered, meet and attempt in good faith to resolve such Commercial License Grant Dispute. If such Commercial License Grant Dispute is not resolved within such 20-day period, either Party may require that the Parties submit such Commercial License Grant Dispute for resolution by an independent Third Party with appropriate qualifications for resolution to evaluate such matter (a "***Neutral Expert***") by providing a written notice (an "***External Commercial License Grant Dispute Resolution Notice***") to such effect that identifies the Commercial License Grant Dispute to be resolved to the other Party within 15 days after the end of

such 20-day period. If the Parties fail to agree on a Neutral Expert within 10 days after an External Commercial License Grant Dispute Resolution Notice is delivered, then each Party will submit the name and qualifications of one proposed Neutral Expert, along with a written statement not to exceed five pages that identifies the issue(s) to be decided, to JAMS in Denver, Colorado, pursuant to its Streamlined Arbitration Rules and Procedures, with a copy to the other Party, and JAMS will appoint a single arbitrator, who will be authorized solely to select, within 10 days of his or her appointment and pursuant to this Section 10(e), which Party's proposed Neutral Expert will be designated for resolution of such matter, which decision will be final and binding on both Parties. Upon the designation of the Neutral Expert, each Party will have 10 days to submit any appropriate materials to such Neutral Expert, with copies to the other Party. No Party will communicate with the Neutral Expert except by written communications copied to the other Party, or orally in the physical or telephonic presence of the other Party. The Neutral Expert will render a written decision within 15 days after the deadline for submission of materials from the Parties. The decision of the Neutral Expert will be final and binding on both Parties. The Parties agree that any and all such deliberations will be confidential.

(f) **Grants of Non-Exclusive Licenses Under Disclaimed Patentable Project Intellectual Property.**

(i) **Grant of Non-Exclusive License to the Foundation.** With respect to each patent (including (A) any patent application, divisional, continuation, continuation-in-part, substitute, renewal, reexamination, extension or reissue in respect of such patent or (B) any intellectual property rights claimed in respect of such patent) claiming Patentable Project HD Intellectual Property that the Foundation has disclaimed its interest pursuant to Section 9(e) of this Agreement (the "***Foundation Disclaimed Intellectual Property***"), Isis hereby grants the Foundation a fully paid-up, royalty-free, irrevocable, perpetual, worldwide non-exclusive license, with the limited right to sublicense as set forth in this Section 10(f)(i), under such Foundation Disclaimed Intellectual Property for HD Research and Development, including a license to (1) make, have made, use, have used, import and have

imported any product covered by such Foundation Disclaimed Intellectual Property, (2) practice and have practiced any method or process covered by such Foundation Disclaimed Intellectual Property, and (3) use and have used the Confidential Information relating to such Foundation Disclaimed Intellectual Property, in each case solely for HD Research and Development. The foregoing license a) will be for HD Research and Development only, b) will not include any right to manufacture or distribute for sale or sell, c) will not be subject to royalties or other fees and d) will include the right to grant sublicenses on the same terms; *provided*, *that*, such sublicense 1) is granted without payment of royalties, other fees or profit and 2) prohibits the sublicensee from granting sublicenses.

(ii) **Grant of Non-Exclusive License to Isis.** With respect to each patent (including (A) any patent application, divisional, continuation, continuation-in-part, substitute, renewal, reexamination, extension or reissue in respect of such patent or (B) any intellectual property rights claimed in respect of such patent) claiming Patentable Project HD Intellectual Property that Isis has disclaimed its interest pursuant to Section 9(e) of this Agreement (the "***Isis Disclaimed Intellectual Property***"), the Foundation hereby grants Isis a fully paid-up, royalty-free, irrevocable, perpetual, worldwide non-exclusive license, with the limited right to sublicense as set forth in this Section 10(f)(ii), under such Isis Disclaimed Intellectual Property for Research and Development, including a license to (1) make, have made, use, have used, import and have imported any product covered by such Isis Disclaimed Intellectual Property, (2) practice and have practiced any method or process covered by such Isis Disclaimed Intellectual Property and (3) use and have used the Confidential Information relating to such Isis Disclaimed Intellectual Property, in each case solely for Research and Development. The foregoing license a) will be for Research and Development only, b) will not include any right to manufacture or distribute for sale or sell, c) will not be subject to royalties or other fees and d) will include the right to grant sublicenses on the same terms; *provided*, *that*, such sublicense 1) is granted without payment of royalties, other fees or profit and 2) prohibits the sublicensee from granting sublicenses.

(g) **Grant of Non-Exclusive Licenses Under Isis Background Intellectual Property in Connection with Commercial Licenses.** Subject to the disclosure set forth on Schedule 16(b)(iv)(B) - 2, Isis will grant to each Third Party or Affiliate of a Party that is a party to a Commercial License, in sole consideration for the amounts paid by such Third Party or Affiliate under such Commercial License, a worldwide non-exclusive license (with the right to grant sublicenses to any Affiliate or Third Party collaborator of such licensee, but without the right to grant further sublicenses) under any Isis Background Intellectual Property Controlled by Isis (including (A) any patent application, divisional, continuation, continuation-in-part, substitute, renewal, reexamination, extension or reissue in respect of any applicable patent within such Isis Background Intellectual Property Controlled by Isis or (B) any intellectual property rights claimed in respect of any applicable patent within such Isis Background Intellectual Property Controlled by Isis), to the extent necessary to enable such Third Party or Affiliate to exploit the Project HD Intellectual Property in accordance with the terms of such Commercial License and the terms of this Agreement. Any license granted by Isis to a Third Party or Affiliate of a Party pursuant to this Section 10(g) shall terminate only in accordance with the terms and conditions of the Commercial

License granted to such Third Party or Affiliate. For the avoidance of doubt, any license to Isis Background Intellectual Property Controlled by Isis granted under this Section 10(g) will in no event entitle a licensee under a Commercial License to use such Isis Background Intellectual Property to research, develop or otherwise use or make any compound other than the Project Compound(s) subject to such Commercial License.

11. **Non-Assert Covenants.**

(a) **Mutual Non-Assert Regarding Validity.** Each Party will not, and will not permit its Affiliates to, challenge, nor assist others in challenging, and will undertake to ensure, by contract or otherwise, that its licensees and assignees of any Project Intellectual Property will not challenge nor assist others in challenging, the validity of any Project Intellectual Property (including any Project Intellectual Property that is disclaimed by a Party); *provided*, *however*, that each Party (and its Affiliates, licensees and assignees) has the right to comply with applicable laws, including subpoenas in connection with a challenge by a Third Party to Project Intellectual Property.

(b) **Isis Non-Assert Regarding Infringement.** Isis will not, and will not permit its Affiliates to, bring any action or assist others in bringing any action, and undertakes to ensure, by contract or otherwise, that its licensees and assignees of any Project Intellectual Property (including any Isis Disclaimed Intellectual Property) will not bring any action or assist others in bringing any action, against the Foundation or the Foundation's licensees or assignees of any Project HD Intellectual Property (including any Foundation Collaborator) on the ground that the practice or use, as the case may be, of any Project HD Intellectual Property for HD Research and Development infringes or misappropriates the proprietary rights of Isis or Isis' licensees or assignees of any Project Intellectual Property; *provided*, *however*, that Isis (and its Affiliates, licensees and assignees) has the right to comply with applicable laws, including subpoenas in connection with a challenge by a Third Party to Project HD Intellectual Property.

(c) **Foundation Non-Assert Regarding Infringement.** The Foundation will not, and will not permit its Affiliates to, bring any action or assist others in bringing any action, and undertakes to ensure, by contract or otherwise, that its licensees and assignees of any Project HD Intellectual Property (including any Foundation Disclaimed Intellectual Property) will not bring any action or assist others in bringing any action, against Isis or Isis' licensees or assignees of any Project Intellectual Property on the ground that the practice or use, as the case may be, of any Project Intellectual Property outside the HD Field of Use infringes or misappropriates the proprietary rights of the 'Foundation or the Foundation's licensees or assignees of any Project HD Intellectual Property; *provided*, *however*, that the Foundation (and its Affiliates, licensees and assignees) has the right to comply with applicable laws, including subpoenas in connection with a challenge by a Third Party to Project Intellectual Property.

12. **Grant of Non-Exclusive License to the Foundation Under Isis Background Intellectual Property.** Subject to the disclosure set forth on Schedule 16(b)(iv)(B) - 2, Isis hereby grants to the Foundation a fully paid-up, royalty-free, worldwide non-exclusive license (with the right to grant sublicenses to a Third Party designated by the Foundation, including a Foundation Collaborator) under the Isis Background Intellectual Property Controlled by Isis (including (A) any patent application, divisional, continuation, continuation-in-part, substitute, renewal, reexamination, extension or reissue in respect of any applicable patent within such Isis Background Intellectual Property Controlled by Isis, or (B) any intellectual property rights claimed in respect of any applicable patent within such Isis Background Intellectual Property Controlled by Isis), to the extent necessary to enable the Foundation and/or such Third Party (including Foundation Collaborators) to use the Project Results, any Project Deliverables, any Project HD Intellectual Property and any Project Compound solely for HD Research and Development. The license rights granted by Isis under this Section 12 will be subject to termination by Isis in the event of the Foundation's material breach of this Agreement if such material breach is not cured within 45 days following receipt by Isis of notice of such material breach. For the avoidance of doubt, any license to Isis Background Intellectual Property Controlled by Isis granted under this Section 12 will in no event entitle a licensee to use such Isis Background Intellectual Property to research, develop or otherwise use or make any compound other than the Project Compound(s).

13. **Revenue Sharing.**

(a) **Agreement to Share Revenue.** All revenue (i) received by either of the Parties from a Third Party or an Affiliate of either Party in connection with the grant of any Commercial License (including a Commercial License pursuant to which Isis or an Affiliate of Isis is the Licensee) of any Project HD Intellectual Property (other than Project HD Intellectual Property which has been disclaimed by one of the Parties pursuant to Section 9(e) of this Agreement) to a Third Party or an Affiliate of either Party or (ii) received by Isis from a Third Party or any of Isis' Affiliates in connection with the exploitation of any Reverted Project HD Intellectual Property (including in connection with any sale, transfer, license or other disposition of any such Reverted Project HD Intellectual Property or the sale of any product or service covered by any such Reverted Project HD Intellectual Property to a Third Party or an Affiliate of Isis) ((i) and (ii) immediately above collectively referred to herein as "***Revenue***") will be distributed as follows:

(i) First, to the Parties *pro rata* based upon the amount of Patent Expenses paid by each Party out of the total amount Patent Expenses paid by both of the Parties until the aggregate amount of Patent Expenses paid by each of the Parties has been received by each such Party.

(ii) Second, to the Foundation and Isis equally until an amount equal to the sum of the following amounts has been received by the Foundation:

(A) an amount equal to US$[***] (such amount representing the aggregate payments made by the Foundation to Isis and Affiliates of Isis under the 2007 Research Agreement) plus

(B) the aggregate amount of payments made by the Foundation to Isis under that certain Letter Agreement, dated as of [***], between Isis and the Foundation related to [***] (as amended from time to time) plus

(C) the aggregate amount of payments made by the Foundation to Isis and Affiliates of Isis under this Agreement (as amended from time to time), including all amounts paid by the Foundation to Isis to reimburse Isis for Isis Provided Reimbursable Materials Costs and Specialized Licenses or Services Costs plus

(D) the aggregate of the amounts set forth on Schedule 13(a)(ii)(D) attached hereto (each such amount representing a prior payment(s) made by the Foundation to a Third Party or Affiliate of Isis for the development of the Project HD Intellectual Property as a therapeutic product for Huntington's disease patients) plus

(E) the aggregate amount of payments made by the Foundation to Third Parties and Affiliates of Isis for research and development activities related to developing the Project HD Intellectual Property as a therapeutic product for Huntington's disease patients that (1) are set forth on Schedule 13(a)(ii)(E) attached hereto or (2) have been approved by the Steering Committee (any such agreement to be set forth in the applicable mutually-approved Steering Committee meeting minutes) plus

(F) [***].

(iii) Thereafter, 100% of all Revenue to Isis.

(b) **Amounts not Subject to Revenue Sharing.**

(i) **Revenue Sharing only Applicable to Amounts Received by either Party in Connection with Commercial License Granted to Third Parties and Affiliates.** For the avoidance of doubt, the Parties agree that this Section 13 will only apply to Revenue received by either of the Parties.

(ii) **No Revenue Sharing for Amounts Received by Isis in Connection with Research and Development of the Project HD Intellectual Property.** For the avoidance of doubt, the Parties agree that this Section 13 will only apply to Revenue and will not apply to any amounts received by Isis so

long as any such amounts are paid (x) solely to reimburse Isis for the actual internal costs and expenses incurred by Isis from the use of Project HD Intellectual Property for Research and Development conducted internally by Isis or (y) for the use or other exploitation (including the grant of any license for any purpose) of any Project HD Intellectual Property outside the HD Field of Use.

(c) **Relation to Revenue Sharing under the 2007 Research Agreement.** Isis and the Foundation agree that this Section 13 supersedes and replaces in its entirety Section 11 of the 2007 Research Agreement.

Confidentiality; Trademarks

14. **Certain Information Deemed Confidential Information; Certain Information Specifically Excepted from Being Deemed Confidential Information; Permitted Uses of Confidential Information; Confidentiality and Non-Use; Use by Representatives; Exceptions to Confidentiality and Non-Use.**

(a) **Certain Information Deemed Confidential Information; Certain Information Specifically Excepted from Being Deemed Confidential Information.**

(i) **Certain Information Deemed Confidential Information.**

(A) **Certain Information Deemed Confidential Information of Isis.** The Foundation agrees that all Isis Background Intellectual Property will be deemed Confidential Information of Isis (the foregoing, together with any additional information disclosed by Isis in accordance with clause (i) of the first sentence of Section 1(p) of this Agreement (except to the extent that any such information constitutes Project Intellectual Property or Project Results), the "***Isis Confidential Information***").

(B) **Certain Information Deemed Confidential Information of the Foundation.** Isis agrees that all Foundation Provided Material Information and Foundation Background Intellectual Property will be deemed Confidential Information of the Foundation (the foregoing, together with such additional information disclosed by the Foundation in accordance with clause (i) of the first sentence of Section 1(p) of this Agreement (except to the extent that any such information constitutes Project Intellectual Property or Project Results), the "***Foundation Confidential Information***").

(C) **Certain Information Deemed Confidential Information of both Parties.** The Parties agree that (1) the terms and conditions of this Agreement (including all appendices, supplements or exhibits attached to this Agreement) and all Project Intellectual Property

and Project Results (including all Project Results set forth in the Project Reports) will be deemed Confidential Information of both Parties ("***Joint Confidential Information***") and (2) each Party will be deemed both a "Disclosing Party" and a "Receiving Party" of all Joint Confidential Information. The Parties further agree to treat all Joint Confidential Information as Confidential Information of each of the Parties in accordance with the terms of this Section 14. Notwithstanding the foregoing, the Parties agree after the sixth anniversary of the Original Effective Date (the "***Disclosure Date***") the Project Results shall no longer be deemed Confidential Information and may be disclosed by either Party to any Affiliate or Third Party without restriction unless prior to the Disclosure Date Isis notifies the Foundation that there exists good reasons for such disclosure to be withheld for an additional six-month period, in which case the Disclosure Date will be extended for an additional six months and the provisions of this Section 14(a)(i)(C) will apply to such new Disclosure Date.

(ii) **Certain Information Specifically Excepted from Being Deemed Confidential Information.** For the avoidance of any doubt, the Parties acknowledge and agree that any information deemed to be Confidential Information pursuant to Section 14(a)(i) of this Agreement will not constitute Confidential Information under this Agreement if such information constitutes information which is specifically excepted from being Confidential Information in accordance with Section 1(p) of this Agreement; *provided*, *however*, the Parties acknowledge and agree that no Joint Confidential Information will be specifically excepted from being Confidential Information pursuant to clause (1) of the last sentence of Section 1(p) of this Agreement.

(b) **Permitted Uses of Confidential Information.**

(i) **Permitted Uses of Joint Confidential Information.**

(A) **Permitted Uses of Joint Confidential Information by Isis.** The Foundation agrees that Isis may (1) use, or have used, the Joint Confidential Information for all uses and purposes to the extent necessary or useful to enable Isis to perform its obligations or exercise its rights under this Agreement and (2) subject to Section 14(c) of this Agreement, disclose the Joint Confidential Information to Third Parties and Affiliates of Isis.

(B) **Permitted Uses of Joint Confidential Information by the Foundation.** Isis agrees that the Foundation may (1) use, or have used, the Joint Confidential Information for all uses and purposes to the extent necessary or useful to enable Isis to perform its

obligations or exercise its rights under this Agreement and (2) subject to Section 14(c) of this Agreement, disclose the Joint Confidential Information to Third Parties and Affiliates of the Foundation.

(ii) **Permitted Uses of Foundation Confidential Information by Isis.** Isis agrees that the Foundation Confidential Information may only (A) be used by Isis to the extent necessary or useful to enable Isis to perform its obligations or exercise its rights under this Agreement and (B) be disclosed in accordance with, and to only those Third Parties and Affiliates expressly permitted by, Section 14(c) of this Agreement.

(iii) **Permitted Uses of Isis Confidential Information by the Foundation.** The Foundation agrees that Isis Confidential Information may only (A) be used by the Foundation to the extent necessary or useful to enable the Foundation to perform its obligations or exercise its rights under this Agreement and (B) be disclosed in accordance with, and to only those Third Parties and Affiliates expressly permitted by, Section 14(c) of this Agreement.

(c) **Confidentiality and Non-Use; Use by Representatives.**

(i) **Confidentiality and Non-Use.** Each Receiving Party will treat the Confidential Information of the Disclosing Party in the same manner, and with the same level of care (but, in no event, with less than a reasonable level of care), as the Receiving Party would treat its own confidential or proprietary information. Without limiting the generality of the foregoing, and except to the extent expressly permitted by this Agreement (including pursuant to Section 14(b) of this Agreement), no Receiving Party will, without the prior written consent of the Disclosing Party, (A) disclose, reveal, report, publish or give the Confidential Information of the Disclosing Party to any Third Party or Affiliate or (B) use the Confidential Information of the Disclosing Party for any purpose.

(ii) **Use by Representatives.** Except as expressly permitted by this Agreement, each Receiving Party will limit disclosure of the Disclosing Party's Confidential Information to (A) those of its Affiliates, directors, officers, employees, representatives, consultants, agents, service providers and advisors (including scientific advisors, legal counsel, etc.) (B) in the case of Isis only, any Third Party collaborator of Isis and (C) in the case of the Foundation only, the Foundation Collaborators (collectively, "***representatives***") who (1) have a need to know such Confidential Information to enable such Receiving Party to perform its obligations or exercise its rights under this Agreement, (2) have similar, but no less burdensome, obligations of confidentiality and non-use to those contained in this Agreement and (3) have been advised of the confidential and

proprietary nature of such Confidential Information and of their obligations with respect to such Confidential Information. Each Receiving Party will (x) direct its representatives not to disclose the Confidential Information of the Disclosing Party to any person or entity, except as expressly permitted under this Agreement and (y) be responsible for any breach by its representatives of the obligations under this Agreement relating to Confidential Information of the Disclosing Party.

(d) **Exceptions to Confidentiality and Non-Use.** Each Receiving Party may, without the prior written authorization of the Disclosing Party, disclose the Confidential Information of the Disclosing Party to the limited extent it is required to pursuant to any applicable federal, state, local, or international law, or any judicial or government request, requirement or order; provided, that, such Receiving Party provides the Disclosing Party with sufficient prior notice, and cooperates with the Disclosing Party (at such Disclosing Party's cost and expense), to allow the Disclosing Party to contest such request, requirement or order. In addition, each Party may disclose (i) the existence of this Agreement; (ii) a general summary of the Research being provided under this Agreement; (iii) the aggregate dollar amount of fees to be paid by the Foundation under this Agreement; and (iv) any specific terms of this Agreement that are a matter of public record except by breach of this Agreement; provided, that, if Isis determines that applicable securities laws or regulations require it to disclose additional information about this Agreement or its terms or conditions, Isis will notify the Foundation in writing of such disclosure requirement and will cooperate with the Foundation in requesting confidential treatment of any provision of this Agreement as reasonably requested by the Foundation.

(e) **[***] Collaboration**. The Foundation has entered into a collaboration with [***] and [***] related to the development of therapeutics to treat Huntington's disease (the "[***] Project"). Notwithstanding any provision to the contrary in this Agreement, the Foundation will not (i) disclose, reveal or give any Isis Confidential Information or Joint Confidential Information to [***] or [***] or (ii) provide any Project Compounds to [***] or [***], in each case for use in connection with the [***] Project. The Foundation will not (A) disclose, reveal or give any confidential information of any of the parties to the [***] Project to Isis or (B) provide any compounds resulting from the [***] Project to Isis or any of its Affiliates, in each case for use in connection with this Project. The Parties will implement reasonable safeguards, processes and procedures necessary to abide by the obligations in this Section 14(e).

15. **Use of Trademarks.** No Party will use the name, trademarks, logos, physical likeness or other symbol of the other Party (or their employees) for any marketing, advertising, public relations or other purposes without the prior written authorization of the other Party, except that either Party may (a) make reference to the Foundation's funding of the Research and (b) use the other Party's name in any disclosure permitted pursuant to Section 14(d) of this Agreement; *provided, that*, in each case the relationship of the Parties is accurately and appropriately described.

Covenants; Representations and Warranties

16. **Covenants; Representations and Warranties.**

(a) **Covenants.** Isis agrees to each of the following:

(i) **Conduct of the Research; Compliance with Law.** Isis will perform the Research using generally accepted industry standards and practices and in compliance with all applicable federal, state, local, international, health authority and institutional laws, rules, regulations, orders and guidelines.

(ii) **Audit; Access.** At reasonably convenient times and dates and upon reasonable prior notice (in all cases at least 10 business days), (A) the Foundation and its representatives will have the right to audit Isis' compliance with this Agreement and (B) Isis will provide the Foundation and its representatives with reasonable access to the facilities used in the performance of the Research, data and personnel in order to enable the Foundation to assess the status and progress of the Research being performed by Isis.

(iii) **Research Team.** The Research will only be performed by individuals who have assigned to Isis any ownership or other rights they may acquire in any (A) Project Results produced or (B) Project Intellectual Property conceived, discovered, invented, made or first reduced to practice, in each case in the course of the performance of the Research under this Agreement, so that Isis may perform its obligations and convey the rights granted by it under this Agreement. Isis will not permit any individual to perform any Research or review, or have access to, any Project Results, prior to such individual's execution and delivery of the invention assignments required by this Section 16(a)(iii). Isis will cause any such individual to assign any such (1) Project Results produced or (2) Project Intellectual Property conceived, discovered, invented, made or reduced to practice, in each case in the course of the performance of the Research under this Agreement to Isis.

(iv) **Consents, Licenses, Permits and Approvals.** Isis will obtain all consents, permits and other approvals necessary for Isis to perform its obligations and convey the rights granted by it under this Agreement.

(v) **Conflicting Obligations.** Isis will not enter into, any agreement, contract, license or other arrangement that conflicts with Isis' discharge of its obligations under this Agreement or the Foundation's exercise of its rights under this Agreement.

(vi) **Third Party and Affiliate Intellectual Property.** Except for the Isis Background Intellectual Property set forth on Schedule 16(a)(vi), without the prior written consent of the Foundation, Isis will not use or practice any (A) Intellectual Property (1) that is known by Isis to be owned by a Third Party or one of Isis' Affiliates or (2) which is owned by, or licensed to, Isis (or otherwise subject to restrictions on use known to Isis), (B) Acquirer Intellectual Property of any Acquirer of Isis, (C) Isis/[***] Collaboration Intellectual Property or (D) Regulus Intellectual Property, in the performance of the Research, if the use or practice of any such Intellectual Property would be necessary to enable a) licensee under a Commercial License to practice any Project HD Intellectual Property to the extent necessary for such licensee to commercialize one or more Project Compounds under a Commercial License in accordance with the terms of this Agreement or b) the Foundation and the Foundation Collaborators to use any Project Results, Project Deliverables or Project HD Intellectual Property solely for HD Research and Development, *unless* (1) Isis Controls, and at all times retains Control of, such Intellectual Property, (2) except as set forth on Schedule 16(b)(iv)(B) - 2, Isis does not have to obtain the consent of any Third Party or Affiliate or pay any compensation to any Third Party or Affiliate to license or sublicense such Intellectual Property and (3) grants a license or sublicense, as the case may be, in respect of any such Intellectual Property to (a) a licensee under a Commercial License to the extent necessary for such licensee to commercialize one or more Project Compounds under such Commercial License in accordance with the terms of this Agreement, including under Section 10(g) of this Agreement and (b) the Foundation (with the right to grant sublicenses to the Foundation Collaborators), pursuant to the terms and conditions of this Agreement, including Section 12 of this Agreement, to use any Project Results, Project Deliverables or Project HD Intellectual Property solely for HD Research and Development.

(vii) **Further Assurances.** Isis will, at the Foundation's expense, (A) execute such further documents, instruments, licenses and assurances and (B) take such further actions, in each case as the Foundation may reasonably request from time to time to better enable the Foundation to exercise its rights under this Agreement; *provided, that*, such further documents, instruments, licenses, assurances and actions will not materially change either Party's rights or obligations under this Agreement.

(viii) **No Debarment.** Isis will not use a Debarred Individual (as defined below) or Debarred Entity (as defined below) to perform any activities or render any assistance on Isis' behalf relating to activities performed pursuant to this Agreement. A "***Debarred Entity***" is a corporation, partnership or association that has been debarred by the FDA pursuant to 21 U.S.C. §335a (a) or (b) from submitting or assisting in the submission of any drug

product application, or a member, subsidiary or Affiliate of a Debarred Entity; and a "***Debarred Individual***" is an individual who has been debarred by the FDA pursuant to 21 U.S.C. §335a (a) or (b) from providing services in any capacity to a person that has an approved or pending drug product application.

(b) **Representations and Warranties.** Isis hereby represents and warrants to each of the following as of the Effective Date:

(i) **No Debarment.** Isis represents and warrants that it has never been, and is not currently, a Debarred Entity.

(ii) **Consents, Licenses, Permits and Approvals.** Isis has obtained all consents, licenses, permits and other approvals necessary for Isis to enter into this Agreement.

(iii) **Conflicting Obligations.** Neither the execution and delivery of this Agreement by Isis nor the discharge by Isis of its obligations under this Agreement will conflict with, result in a breach of, constitute a default under, require any notice under or create in any Third Party the right to terminate, modify or cancel any agreement, contract, instrument, license or other arrangement to which Isis is or becomes a party or by which it is or becomes bound. Isis has not entered into any agreement, contract, license or other arrangement that conflicts with Isis' discharge of its obligations under this Agreement or the Foundation's exercise of its rights under this Agreement.

(iv) **Intellectual Property.**

(A) **General Intellectual Property.** To the knowledge of Isis, Isis owns or has the right to use pursuant to a valid and enforceable, written license, sublicense, agreement or other permission, all Intellectual Property necessary to perform the Research. To the knowledge of Isis, except as specifically disclosed in that certain letter dated as of the Original Effective Date from Grantland E. Bryce, Vice President, Corporate Development & Legal Counsel to Robi Blumenstein, Isis' performance of the Research will not interfere with, infringe upon, violate or misappropriate any Intellectual Property rights of any Third Party or Affiliate of Isis.

(B) **Isis Background Intellectual Property.** Schedule 16(b)(iv)(B) - 1 sets forth a complete and accurate list of all Isis Background Intellectual Property that is not Controlled by Isis that would be necessary to enable (1) a Third Party licensee under a Commercial License to practice any Project HD Intellectual Property to the extent necessary for such Third Party to commercialize one or

more Project Compounds under a Commercial License in accordance with the terms of this Agreement and (2) the Foundation and the Foundation Collaborators to use the Project Results, any Project Deliverables and Project HD Intellectual Property solely for HD Research and Development. Except as set forth on Schedule 16(b)(iv)(B) - 2, Isis has the right to grant the licenses and sublicenses contemplated by this Agreement to the Isis Background Intellectual Property Controlled by Isis without obtaining the consent of any Third Party or Affiliate and without the payment of any compensation to any Third Party or Affiliate.

(C) **Certain Third Party and Affiliate Intellectual Property.** During the period beginning on the Original Effective Date and ending on the Effective Date, Isis did not use or practice any (A) Intellectual Property (1) that was known by Isis to be owned by a Third Party or one of Isis' Affiliates or (2) which was owned by, or licensed to, Isis (or otherwise subject to restrictions on use known to Isis), (B) Acquirer Intellectual Property of any Acquirer of Isis, (C) Isis/[***] Collaboration Intellectual Property or (D) Regulus Intellectual Property, in the conduct of the 2007 Research Agreement Project, that would be necessary to be used or practiced to enable a) licensee under a Commercial License to practice any Project HD Intellectual Property to the extent necessary for such licensee to commercialize one or more Project Compounds under a Commercial License in accordance with the terms of this Agreement or b) the Foundation and the Foundation Collaborators to use any Project Results, Project Deliverables or Project HD Intellectual Property solely for HD Research and Development, *other than* any such Intellectual Property that Isis (1) Controls, and at all times retains Control of, such Intellectual Property and (2) grants a license or sublicense, as the case may be in respect of any such Intellectual Property to (a) a licensee under a Commercial License to the extent necessary for such licensee to commercialize one or more Project Compounds under such Commercial License in accordance with the terms of this Agreement, including under Section 10(g) of this Agreement and (b) the Foundation (with the right to grant sublicenses to the Foundation Collaborators), pursuant to the terms and conditions of this Agreement, including Section 12 of this Agreement, to use any Project Results, Project Deliverables or Project HD Intellectual Property solely for HD Research and Development.

Term; Termination; Effect of Termination

17. **Term; Termination of Certain Sections by the Foundation; Termination of Certain Sections by Isis; Termination of Specified Sections; Survival of Remaining Sections; Effect of Termination of Certain Sections.**

(a) **Term.** The term (the "***Term***") of this Agreement will commence on the Effective Date and will, unless earlier terminated in accordance with the terms hereof or by the mutual written agreement of the Parties, continue in effect until the date that is 30 days after the date on which all activities that have been approved by the Steering Committee to be conducted as part of the Project (as evidenced by such activities being set forth in the Detailed Project Description most recently approved by the Steering Committee) have been completed.

(b) **Termination of Certain Sections by the Foundation.**

(i) **Termination with Notice.** The Foundation may elect for any reason to immediately terminate all of the sections specified in Section 17(d)(i) of this Agreement and discontinue Isis' performance of the Research by giving 60 days prior written notice to such effect to Isis.

(ii) **Termination Upon the Occurrence of Certain Events.** The Foundation may, by giving notice to Isis, elect to terminate each of the sections specified in Section 17(d)(i) of this Agreement and discontinue Isis' performance of the Research upon the occurrence of any of the following events:

(A) **Breach of this Agreement.** If Isis (1) materially breaches any representation, warranty or covenant given by it under this Agreement or (2) materially defaults in the performance of its obligations under this Agreement and such breach or default is not remedied within 45 days of the receipt by Isis of notice of such breach or default from the Foundation.

(B) **Change of Circumstances Notice.** Isis delivers a Change of Circumstances Notice to the Foundation pursuant to Section 3(b)(i) of this Agreement.

(C) **Post-Original Effective Date Knowledge Notice.** If Isis delivers a Post-Original Effective Date Knowledge Notice to the Foundation pursuant to Section 3(b)(ii) of this Agreement.

(D) **Bankruptcy Event.** If Isis is the subject of a Bankruptcy Event.

(c) **Termination of Certain Sections by Isis.** Isis may, by giving notice to the Foundation, elect to terminate each of the sections specified in Section 17(d)(i) of this Agreement and discontinue Isis' performance of the Research upon the occurrence of any of the following events:

(i) **Breach of this Agreement.** If the Foundation (A) materially breaches any representation, warranty or covenant given by it under this Agreement or (B) materially defaults in the performance of any of its obligations under this Agreement and such breach or default is not remedied within 45 days of the receipt by the Foundation of notice of such breach or default from Isis.

(ii) **Bankruptcy Event.** If the Foundation is the subject of a Bankruptcy Event.

(d) **Termination of Specified Sections; Survival of Remaining Sections; Effect of Termination of Certain Sections.**

(i) **Termination of Specified Sections; Survival of Remaining Sections.** Immediately upon the earlier to occur of either (A) the expiration of the Term, (B) the mutual agreement of the Parties to terminate this Agreement, (C) an election by the Foundation pursuant to Section 17(b) of this Agreement or (D) an election by Isis pursuant to Section 17(c) of this Agreement, then subject to Section 17(d)(ii) of this Agreement, each of Section 2, Section 3(a), Section 3(b), Section 4(a), Section 4(b), Section 4(c)(iii), Section 5(a), Section 5(b), Section 6(a) and Section 6(b) will a) immediately terminate and b) subject to Section 17(d)(ii) of this Agreement, have no further force or effect. The Parties acknowledge and agree that in the event of the termination of the sections specified in this Section 17(d)(i), all other sections of this Agreement will survive indefinitely and remain in full force and effect.

(ii) **Effect of Termination of Certain Sections.**

(A) **Delivery of Final Project Reports, Provided Research Materials, Project Deliverables and Project Results.** Upon the termination of the sections specified in Section 17(d)(i) of this Agreement, Isis will deliver to the Foundation each of the following: (1) in accordance with Section 5(e) of this Agreement, a Final Project Report for the Project for the period beginning on the Effective Date through the date of such termination, (2) in accordance with Section 5(e) of this Agreement, a final FTE Report for the period beginning on the end date of the period covered by the last FTE Report delivered through the date of such termination, (3) in accordance with Section 4(c) of this Agreement, all unused Provided Research Materials and (4) in accordance with Section 7(b) and Section 8(b), respectively, of this Agreement, all Project Results and Project Deliverables produced by Isis but not yet delivered to the Foundation through the date of such termination.

(B) **Foundation's Payment Obligation Upon Termination.** The Parties acknowledge and agree that, upon the termination of the sections specified in Section 17(d)(i) of this Agreement, the Foundation will, subject to Section 6 of this Agreement, make a payment (to the extent such payment is not in dispute) (1) in respect of the Research FTEs performing the Research through the effective date of the termination of the sections specified in Section 17(d)(i) of this Agreement (such payment to be calculated in accordance with Section 6 of this Agreement) and (2) to reimburse Isis for any Isis Provided Reimbursable Materials Costs and Specialized Licenses or Services Costs incurred by Isis in accordance with, and subject to, Section 4(b) and Section 4(d) of this Agreement, respectively, unless the obligations of Isis to procure Isis Provided Reimbursable Materials and Specialized Third Party Licenses and Services related to such costs may be cancelled by Isis in which case the Foundation will only reimburse Isis for the contractual cancellation fees associated with the cancellation of such obligations. Isis agrees that a) the invoice submitted by Isis in respect of the final Quarterly Research Payment shall credit the Advance Research Payment Amount against such final Quarterly Research Payment and b) if the amount of final Quarterly Research Payment is less than the Advance Research Payment Amount, Isis shall promptly make a payment to the Foundation in an amount equal to the amount by which the Advance Research Payment Amount exceeded the amount of the final Quarterly Research Payment.

(C) **Facilitation of Continued Research.** Upon the termination of the sections specified in Section 17(d)(i) of this Agreement, if requested by the Foundation, Isis and the Foundation will, in good faith, discuss the use of reasonable efforts to facilitate the continuance of the Project elsewhere.

(D) **Liabilities and Obligations Accrued Prior to Termination.** The Parties acknowledge and agree that the termination of the sections specified in Section 17(d)(i) of this Agreement will not (1) relieve any Party then in breach of this Agreement for any liabilities to the other Party in respect of any breach under this Agreement or (2) relieve either Party from any of the obligations such Party may have under this Agreement to the extent such obligations accrued prior to the date of such termination or (3) relieve either Party from any of the obligations such Party may have under any of the sections of this Agreement that expressly survive any such termination.

Miscellaneous

18. **Independent Contractor.** Isis is acting as an independent contractor and not an agent, joint venturer or partner of the Foundation. Nothing in this Agreement will create, evidence or imply any agency, partnership or joint venture between the Parties. Neither Party will act or describe itself as the agent of the other Party nor will it represent that it has any authority to make commitments on the other Party's behalf.

19. **Notices.** Any notice required or permitted to be given by this Agreement will be in writing and will be delivered by personal delivery, US mail with postage prepaid and return receipt requested, facsimile (provided the sender has evidence of successful transmission) or next-day courier service. Any notice so delivered will be deemed to be given, delivered and received, if delivered by personal delivery or if delivered by US mail, on the day received as indicated by the postal receipt and if delivered by facsimile or courier service, on the day following dispatch. All such notices are to be given or made at the following addresses (or to such other address as may be designated by a notice given in accordance with the provisions of this Section 19):

If to the Foundation to:

CHDI Foundation, Inc.
c/o CHDI Management, Inc.
350 Seventh Avenue, Suite 601
New York, NY 10001
Attention: Ruth Basu, Chief Administrative Officer
Fax: 212-239-2101

With a copy to:

CHDI Foundation, Inc.
c/o CHDI Management, Inc.
350 Seventh Avenue, Suite 601
New York, NY 10001
Attention: David P. Rankin, Chief Legal Officer
Fax: 212-239-2101

If to Isis **prior to August 22, 2011**, to:

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008
Attention: C. Frank Bennett, Ph.D.
Fax: 760-603-4650

With copies to:

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008
Attention: Chief Operating Officer & Chief Financial Officer
Fax: 760-918-3592

and

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008
Attention: Vice President, Legal & General Counsel
Fax: 760-268-4922

If to Isis **on or after August 22, 2011**, to:

Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: C. Frank Bennett, Ph.D.
Fax: 760-603-4650

With copies to:

Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: Chief Operating Officer & Chief Financial Officer
Fax: 760-918-3592

and

Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: Vice President, Legal & General Counsel

20. Indemnity; Limitation on Damages.

(a) Indemnification by the Foundation. The Foundation will defend and indemnify Isis, its Affiliates and their respective directors, officers, employees, representatives, consultants, agents and service providers (collectively, the "***Isis Indemnified Parties***"), against any and all costs, damages, expenses (including reasonable legal fees) and losses suffered by any Isis Indemnified Party in

connection with any Third Party action, assessment, claim, demand, proceeding or suit to the extent arising or resulting from (i) the Foundation's negligence or willful misconduct; (ii) the Foundation's breach of this Agreement; (iii) Isis' use, or alleged use, in the performance of the Research of any Foundation Provided Materials or Foundation Provided Material Information provided by the Foundation to Isis for the purpose of performing the Research; or (iv) the storage, distribution or use of a Project Compound by the Foundation or any Foundation Collaborator (but in each case only to the extent such claim does not result from, or arise out of, an action for which Isis is obligated to indemnify the Foundation pursuant to Section 20(b) of this Agreement). For clarity, the Parties agree that the parenthetical clause in the immediately preceding sentence is not intended to obviate or otherwise limit the possibility that both Isis and the Foundation may be determined to be joint tort-feasors and, therefore, share liability.

(b) Indemnification by Isis. Isis will defend and indemnify the Foundation and its Affiliates, members, directors, officers, employees, representatives, consultants, agents and service providers (collectively, the "***Foundation Indemnified Parties***"), against any and all costs, damages, expenses (including reasonable legal fees) and losses suffered by any Foundation Indemnified Party in connection with any Third Party action, assessment, claim, demand, proceeding or suit to the extent arising or resulting from (i) Isis' negligence or willful misconduct; (ii) Isis' breach of this Agreement; (iii) the storage, distribution or use of a Project Compound by Isis or any collaborator of Isis (other than the Foundation) or (iv) the activities of Isis in the course of Isis' performance of the Research, including activities which infringe upon, violate or misappropriate, or are alleged to infringe upon, violate or misappropriate, the Intellectual Property rights of a Third Party (but (A) excluding all activities that infringe upon, violate or misappropriate, or are alleged to infringe upon, violate or misappropriate, the Intellectual Property rights of a Third Party if (1) in accordance with Section 16(a)(vi) of this Agreement, the Foundation consented to the use or practice, as the case may be, of such Third Party Intellectual Property by Isis in the conduct of such activities or (2) in accordance with Section 3(b)(ii) of this Agreement, Isis notified the Foundation with respect to the to the use or practice, as the case may be, of such Third Party Intellectual Property by Isis in the conduct of such activities and the Foundation did not exercise, within 90 days of the Foundation's receipt of Isis' notice, its right to terminate the applicable Project(s) or this Agreement and (B) only to the extent such claim does not result from, or arise out of, an action for which the Foundation is obligated to indemnify Isis pursuant to Section 20(a) of this Agreement). For clarity, the Parties agree that the parenthetical clause in the immediately preceding sentence is not intended to obviate or otherwise limit the possibility that both Isis and the Foundation may be determined to be joint tort-feasors and, therefore, share liability.

(c) Limitation on Damages; Damages Cap.

(i) Limitation on Damages. NOTWITHSTANDING ANY OTHER PROVISION OF THIS AGREEMENT BUT SUBJECT TO SECTION 20(d) OF THIS AGREEMENT, NEITHER PARTY NOR ITS AFFILIATES WILL BE LIABLE TO THE OTHER PARTY OR ITS AFFILIATES FOR ANY CONSEQUENTIAL, SPECIAL, INDIRECT, INCIDENTAL, PUNITIVE OR EXEMPLARY DAMAGES OR OTHER SIMILAR OR LIKE DAMAGES (INCLUDING LOSS OF PROFITS) UNDER THIS AGREEMENT EVEN IF SUCH PARTY OR AFFILIATE HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES; *PROVIDED, THAT*, NOTHING IN THIS AGREEMENT WILL EXCLUDE OR LIMIT THE LIABILITY OF EITHER PARTY FOR (A) A BREACH OF SECTION 14 OF THIS AGREEMENT; (B) DEATH OR PERSONAL INJURY; OR (C) FRAUD.

(ii) Damages Cap. Isis' liability to the Foundation under this Agreement and the 2007 Research Agreement shall not exceed the sum of (A) US$[***] plus (B) [***]. The Foundation's liability to Isis under this Agreement and the 2007 Research Agreement shall not exceed [***]. Isis and the Foundation agree that this Section 20(c)(ii) supersedes and replaces in its entirety Section 18(c)(ii) of the 2007 Research Agreement.

(d) Indemnity Amounts. Any amounts owing pursuant to a Party's express indemnity obligations under this Agreement will not be subject to the limitation on damages restrictions set forth in Section 20(c) of this Agreement.

(e) Indemnity Procedures. In the event that a Party that is entitled to indemnification under Section 20(a) or Section 20(b) of this Agreement, as the case may be (such Party the "***Indemnified Party***") seeks indemnification from the other Party (such Party an "***Indemnifying Party***"), the Indemnified Party will (i) inform, in writing, the Indemnifying Party of the claim as soon as reasonably practicable after the Indemnified Party receives notice of such claim; (ii) permit the Indemnifying Party to assume direction and control of the defense of such claim (including the sole right to settle such claim in the Indemnifying Party's sole discretion, *provided that* any such settlement does not (A) admit any fault or negligence on the part of the Indemnified Party, (B) impose any obligation on the Indemnified Party or (C) without the prior written consent of the Indemnified Party (which consent shall not unreasonably withheld, conditioned or delayed), adversely affect the Indemnified Party in any way; (iii) cooperate as reasonably requested (at the cost and expense of the Indemnifying Party) in the defense of such claim; and (iv) undertake commercially (at the cost and expense of the Indemnifying Party) reasonable steps to mitigate any loss, damage or expense with respect to such claim. Notwithstanding anything in this Agreement to the contrary, the Indemnifying Party will have no liability under Section 20(a) or Section 20(b), of this Agreement, as the case may be, with respect to any claims settled by the Indemnified Party without the Indemnifying Party's prior written consent.

21. Alternative Dispute Resolution.

(a) General. Except for (i) Steering Committee Disputes which are to be resolved pursuant to Section 5(a)(iii)(B) of this Agreement and (ii) Commercial License Grant Disputes which are to be resolved pursuant to Section 10(e) of this Agreement, if a dispute arises out of or relates to this Agreement, or breach thereof, the Parties agree that such dispute will be resolved exclusively in accordance with this Section 21.

(b) Resolution by Good Faith Negotiations. If a dispute arises out of or relates to this Agreement, or breach thereof, the Parties agree to negotiate in good faith to settle such dispute in accordance with this Section 21(b). If a dispute arises out of or relates to this Agreement, or breach thereof, either Party may submit such dispute to B. Lynne Parshall, in the case of Isis (or such other individual identified in writing by Isis), and Robi Blumenstein, in the case of the Foundation (or such other individual identified in writing by the Foundation), for resolution by providing a written notice (each, a "***Senior Management Dispute Resolution Notice***") to the other Party setting forth in reasonable detail the basis of such dispute. If a dispute that is the subject of a Senior Management Dispute Resolution Notice is not resolved by the Parties within 60 days of the delivery of such Senior Management Dispute Resolution Notice, such dispute will be resolved in accordance with Section 21(c) of this Agreement. The Parties agree that any and all such negotiations will be confidential.

(c) Resolution by Binding Arbitration. If a dispute that is the subject of a Senior Management Dispute Resolution Notice is not resolved by the Parties within 60 days of the delivery of such Senior Management Dispute Resolution Notice, either Party may submit such dispute for final resolution by an arbitrator in accordance with this Section 21(c) by providing a written notice (each, an "***Arbitration Dispute Resolution Notice***") to the other Party to such effect within 30 days after the end of such 60-day period. The Parties agree that any dispute that is the subject of an Arbitration Dispute Resolution Notice will be settled by a single arbitrator in a binding arbitration in Denver, Colorado administered by JAMS under its Comprehensive Arbitration Rules and Procedures. The Parties will instruct the arbitrator that the prevailing party of any dispute (as determined by the arbitrator) will be awarded the reasonable attorneys' fees, costs and other expenses incurred by the prevailing party in the course of the arbitration of such dispute. The award rendered by the arbitrator will be final and binding on the Parties, and judgment on the award may be entered in any court having jurisdiction thereof if reasonably necessary for enforcement. The Parties agree that, notwithstanding anything to the contrary in such rules, any and all such proceedings will be confidential.

22. Assignment. Isis may not assign this Agreement without the prior written consent of the Foundation, except to an (a) Affiliate of Isis, or (b) entity that acquires all or substantially all of the business of Isis (whether by sale of assets or stock or by merger or other business combination), and in each case who agrees, in writing, to assume Isis' obligations under this Agreement. Isis agrees that any such assignee will (i) acquire Isis' interest in all of the Isis Background Intellectual Property, Project Compounds, Project Intellectual Property and Project Results and (ii) agree, in writing, to assume Isis' obligations under this Agreement. The Foundation may assign this Agreement so long as the assignee expressly assumes in writing the Foundation's obligations in this Agreement.

23. Press Releases. Upon execution of this Agreement, the Parties will mutually agree to issue either a joint press release or separate press releases announcing the existence of this Agreement, in any case 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, which consent will not be unreasonably withheld or delayed, provided however, that each Party may make disclosures permitted by, and in accordance with, Section 14 of this Agreement. Each Party agrees to provide to the other Party a copy of any public announcement regarding this Agreement or the subject matter thereof as soon as reasonably practicable under the circumstances prior to its scheduled release. Except under extraordinary circumstances, each Party will provide the other with an advance copy of any such announcement at least five business days prior to its scheduled release.

24. Incorporation of Appendices, Exhibits and Schedules; Entire Agreement; Amendment. The appendices, exhibits and schedules identified in this Agreement are incorporated herein by reference and made a part hereof. If (a) any terms or conditions of the 2007 Research Agreement, (b) anything in any appendix, exhibit or schedule attached to this Agreement or (c) any notice, invoice or other document delivered by a Party under this Agreement conflicts with any terms or conditions set forth in the body of this Agreement, the terms and conditions set forth in the body of this Agreement will control. This Agreement constitutes the entire agreement among the Parties relating to the Research and all prior understandings and agreements relating to the Research are superseded hereby. This Agreement may not be amended except by a document signed by authorized representatives of each of the Parties.

25. No Waiver. Any failure of a Party to enforce any provision of this Agreement will not be deemed a waiver of its right to enforce such provision on any subsequent occasion. No waiver of any provision of this Agreement will be valid unless it is in writing and is executed by the Party against whom such waiver is sought to be enforced. A waiver by any of the Parties of any provision of this Agreement will not be construed to be a waiver of any succeeding breach thereof or of any other provision of this Agreement.

26. Severability. Whenever possible, each provision of this Agreement will be interpreted in such manner as to be effective and valid under applicable law. In the event a court of competent jurisdiction holds any provision of this Agreement to be invalid, such holding will have no effect on the remaining provisions of this Agreement, and they will continue in full force and effect.

27. Interpretation; Headings. The word "including" will mean "including without limitation". All pronouns and any variations thereof refer to the masculine, feminine or neuter, singular or plural, as the context may require. All terms defined in this Agreement in their singular or plural forms have correlative meanings when used herein in their plural or singular forms, respectively. Headings used in this Agreement are for convenience of reference only and are not intended to influence the interpretation hereof.

28. **Governing Law.** This Agreement will be governed by and construed in accordance with the domestic laws of the State of New York without giving effect to any choice or conflict of law provision or rule (whether of the State of New York or any other jurisdiction) that would cause the application of the laws of any jurisdiction other than the State of New York.

29. **No Strict Construction.** The Parties have participated jointly in the negotiation and drafting of this Agreement. In the event of an ambiguity or question of intent or interpretation arises, this Agreement will be construed as if drafted jointly by the Parties, and no presumption or burden of proof will arise favoring or disfavoring any of the Parties by virtue of the authorship of any of the provisions of this Agreement.

30. **Counterparts.** This Agreement may be signed, including by facsimile signature, in two or more counterparts and each such counterpart will constitute an original document and such counterparts, taken together, will constitute the same instrument.

In witness to the foregoing, the Parties have executed this Agreement as of the Effective Date.

FOUNDATION:

CHDI Foundation, Inc.

By: /s/ Robi Blumenstein
Name: Robi Blumenstein
Title: President, CHDI Management

ISIS:

Isis Pharmaceuticals, Inc.

By: /s/ B. Lynne Parshall
Name: B. Lynne Parshall
Title: Chief Operating Officer & CFO

Appendix A to Research Agreement

(General Project Description)

Appendix A-1 to Research Agreement

[***]

Appendix A-2 to Research Agreement

[***]

Appendix A-3 to Research Agreement

[***]

Appendix B to Research Agreement

(Initial Detailed Project Description)

Appendix B-1 to Research Agreement

[***]

Appendix B-2 to Research Agreement

[***]

Appendix B-3 to Research Agreement

[***]

Appendix C to Research Agreement

(Additional Project Activities Description)

Schedule 13(a)(ii)(D)

(Schedule of Prior Payments Made by the Foundation to a Third Party of Affiliate of Isis)

[***]

Schedule 13(a)(ii)(E)

(Schedule of Approved Payments to be Made by the Foundation)

[***]

Schedule 16(a)(vi)

(Third Party Intellectual Property)

[***]

Schedule 16(b)(iv)(B) – 1

(Required Isis Background Intellectual Property — Not Controlled by Isis)

[***]

Schedule 16(b)(iv)(B) – 2

[***]

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 7, 2011

/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 7, 2011

/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, 2010, to which this Certification is attached as Exhibit 32.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

2. The information contained in the Periodic Report fairly presents, in all material respects, the financial condition of the Company at the end of the period covered by the Periodic Report and the results of operations of the Company for the period covered by the Periodic Report.

Dated: November 7, 2011

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

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