UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

Form 10-Q

(Mark One)

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

For the Quarterly Period Ended June 30, 2012

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 August 1, 2012 was 100,603,769.

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.

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)

	June 30, 2012 (Unaudited)	December 31, 2011
ASSETS		
Current assets:		
Cash and cash equivalents	$ 85,645	$ 65,477
Short-term investments	250,384	278,187
Contracts receivable	1,558	6,921
Inventories	7,108	4,139

Other current assets	5,724	5,415
Total current assets	350,419	360,139
Property, plant and equipment, net	94,008	96,615
Licenses, net	7,806	9,036
Patents, net	17,701	16,259
Deposits and other assets	2,460	2,845
Total assets	$ 472,394	$ 484,894
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 6,194	$ 8,300
Accrued compensation	4,939	9,183
Accrued liabilities	15,619	18,655
Current portion of long-term obligations	5,313	3,390
Current portion of deferred contract revenue	22,998	36,584
Total current liabilities	55,063	76,112
Long-term deferred contract revenue	31,715	17,474
$2^5/_8$ percent convertible subordinated notes	146,031	141,448
Long-term obligations, less current portion	9,503	4,125
Long-term financing liability for leased facility	70,205	69,877
Investment in Regulus Therapeutics Inc.	5,563	4,424
Total liabilities	318,080	313,460
Stockholders' equity:		
Common stock, $0.001 par value; 200,000,000 shares authorized, 100,320,445 and 100,042,976 shares issued and outstanding at June 30, 2012 and December 31, 2011, respectively	100	100
Additional paid-in capital	1,019,936	1,013,592
Accumulated other comprehensive gain (loss)	968	(770)
Accumulated deficit	(866,690)	(841,488)
Total stockholders' equity	154,314	171,434
Total liabilities and stockholders' equity	$ 472,394	$ 484,894

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 June 30,		Six Months Ended June 30,	
	2012	2011	2012	2011
Revenue:				
Research and development revenue under collaborative agreements	$ 47,140	$ 24,305	$ 68,957	$ 44,319
Licensing and royalty revenue	200	518	1,618	1,651
Total revenue	47,340	24,823	70,575	45,970
Expenses:				
Research and development	40,435	36,009	79,149	70,254
General and administrative	3,209	2,874	6,185	5,884
Total operating expenses	43,644	38,883	85,334	76,138
Income (loss) from operations	3,696	(14,060)	(14,759)	(30,168)
Other income (expense):				
Equity in net loss of Regulus Therapeutics Inc.	(163)	(1,033)	(1,139)	(1,889)
Investment income	477	616	1,077	1,321
Interest expense	(5,219)	(3,437)	(10,398)	(6,851)
Gain (loss) on investments, net	2	34	19	(285)
Loss before income tax expense	(1,207)	(17,880)	(25,200)	(37,872)
Income tax expense	—	(9)	(2)	(11)
Net loss	$ (1,207)	$ (17,889)	$ (25,202)	$ (37,883)
Basic and diluted net loss per share	$ (0.01)	$ (0.18)	$ (0.25)	$ (0.38)
Shares used in computing basic and diluted net loss per share	100,213	99,602	100,185	99,586

See accompanying notes.

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ISIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF COMPREHENSIVE INCOME (LOSS)
(in thousands)
(Unaudited)

	Three Months Ended June 30,		Six Months Ended June 30,	
	2012	2011	2012	2011
Net loss	$ (1,207)	$ (17,889)	$ (25,202)	$ (37,883)
Unrealized gains (losses) on securities	1,210	(290)	1,738	(550)
Comprehensive income (loss)	$ 3	$ (18,179)	$ (23,464)	$ (38,433)

See accompanying notes.

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

	Six Months Ended June 30,	
	2012	2011
Net cash used in operating activities	$ (9,288)	$ (66,019)
Investing activities:		
Purchases of short-term investments	(116,653)	(208,723)
Proceeds from the sale of short-term investments	142,681	298,177
Purchases of property, plant and equipment	(864)	(5,982)
Acquisition of licenses and other assets, net	(1,592)	(1,755)
Purchases of strategic investments	—	(359)
Net cash provided by investing activities	23,572	81,358
Financing activities:		
Proceeds from issuance of equity	1,617	876
Proceeds from equipment financing arrangement	9,100	1,625
Principal payments on debt and capital lease obligations	(4,833)	(2,870)
Net cash (used in) provided by financing activities	5,884	(369)
Net increase in cash and cash equivalents	20,168	14,970
Cash and cash equivalents at beginning of period	65,477	70,052
Cash and cash equivalents at end of period	$ 85,645	$ 85,022
Supplemental disclosures of cash flow information:		
Interest paid	$ 2,275	$ 2,398
Income taxes paid	$ —	$ 2
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 679	$ 1,080
Capitalized costs and financing liability associated with leased facility	$ —	$ 48,575

See accompanying notes.

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ISIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
June 30, 2012
(Unaudited)

1. Basis of Presentation

The unaudited interim condensed consolidated financial statements for the three and six month periods ended June 30, 2012 and 2011 have been prepared on the same basis as the audited financial statements for the year ended December 31, 2011. The financial statements include all normal recurring adjustments, which we consider necessary for a fair presentation of our financial position at such dates and our 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, 2011 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 subsidiary, Symphony GenIsis, Inc., which is currently inactive. 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. 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 consolidated balance sheet.

Research and development revenue under collaborative agreements

Our collaboration agreements typically contain multiple elements, or deliverables, including technology licenses or options to obtain technology licenses, research and development services, and in certain cases manufacturing services. Our collaborations may provide for various types of payments to us including upfront payments, funding of research and development, milestone payments, licensing fees, profit sharing and royalties on product sales. We evaluate the deliverables in our collaboration agreements to determine whether they meet the criteria to be accounted for as separate units of accounting or whether they should be combined with other deliverables and accounted for as a single unit of accounting. When the delivered items in an arrangement have "stand-alone value" to our customer, we account for the deliverables as separate units of accounting and we allocate the consideration to each unit of accounting based on the relative selling price of each deliverable. We use the following hierarchy of values to estimate the selling price of each deliverable: (i) vendor-specific objective evidence of fair value; (ii) third-party evidence of selling price; and (iii) best estimate of selling price, or BESP. The BESP reflects our best estimate of what the selling price would be if we regularly sold the deliverable on a stand-alone basis. We recognize the revenue allocated to each unit of accounting as we deliver the related goods or services. If we determine that we should treat the deliverables as a single unit of accounting, then we recognize the revenue ratably over our estimated period of performance.

Occasionally, we must estimate our period of performance when the agreements we enter 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. 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 not had a material impact on our revenue.

In January 2012, we entered into a collaboration agreement with Biogen Idec to develop and commercialize ISIS-SMN$_{Rx}$ for Spinal Muscular Atrophy, or SMA. As part of the collaboration, we received a $29 million upfront payment and we are responsible for global development of ISIS-SMN$_{Rx}$ through completion of Phase 2/3 registrational clinical trials. Biogen Idec has the option to license ISIS-SMN$_{Rx}$ through completion of the first successful Phase 2/3 trial. If Biogen Idec exercises its option, it will pay us a license fee and will assume global development, regulatory and commercialization responsibilities. We evaluated the delivered item, the option to

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license ISIS-SMN$_{Rx}$, to determine if it had stand-alone value. We determined that the option did not have stand alone value because Biogen Idec cannot pursue the development or commercialization of ISIS-SMN$_{Rx}$ until it exercises the option. As such we considered the deliverables in this collaboration to be a single unit of accounting and we are recognizing the upfront payment over the four-year research and development term for ISIS-SMN$_{Rx}$, which is the estimated period of our performance.

In June 2012, we entered into a separate collaboration agreement with Biogen Idec to develop and commercialize a novel antisense drug targeting DMPK, or dystrophia myotonica-protein kinase. As part of the collaboration, we received a $12 million upfront payment and we are responsible for global development of the drug through the completion of Phase 2 clinical trials. Biogen Idec has the option to license the drug through completion of the Phase 2 trial. If Biogen Idec exercises its option, it will pay us a license fee and will assume global development, regulatory and commercialization responsibilities. We evaluated the delivered item, the option to license the drug, to determine if it had stand-alone value. We determined that the option did not have stand alone value because Biogen Idec cannot pursue the development or commercialization of the drug until it exercises the option. As such we considered the deliverables in this collaboration to be a single unit of accounting and we are recognizing the upfront payment over the five-year research and development term, which is the estimated period of our performance.

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 and/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.

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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 a Marketing Authorization Application, or MAA, 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 have determined that all future development, regulatory and commercialization milestones are substantive. For example, for our strategic alliance with GlaxoSmithKline, or 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 2012, the FDA accepted the NDA for KYNAMRO™. In 2011, we initiated a Phase 1 clinical study on ISIS-TTR_{RX}, the first drug selected as part of our collaboration with GSK, and we selected ISIS-AAT_{RX} as the second development candidate as part of that collaboration. We consider milestones related to progression of a drug through the development and regulatory stages of its life cycle to be substantive milestones because the level of effort and inherent risk associated with these events is high. Therefore, we recognized the entire $25 million milestone payment from Genzyme, a Sanofi Company, in the second quarter of 2012 and the two $5 million milestone payments from GSK in their entirety in 2011. Further information about our collaborative arrangements can be found in Note 7, *Collaborative Arrangements and Licensing Agreements*, below and Note 8 of our audited financial statements for the year ended December 31, 2011 included in our Annual Report on Form 10-K filed with the SEC.

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.

Cash, cash equivalents and short-term investments

We consider all liquid investments with maturities of 90 days or less when we purchase them 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.

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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. If 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.

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-offs for the first six months of 2012 and 2011. Total inventory, which consisted of raw materials, was $7.1 million and $4.1 million as of June 30, 2012 and December 31, 2011, 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 useful lives, beginning with the date the United States Patent and Trademark Office, or foreign equivalent, issues the patent and ending when the patent expires or is written off. For the first six months of 2012 and 2011, we recorded non-cash charges of $288,000 and $801,000, respectively, which we included in research and development expenses, related to the write-down of our patent costs to their estimated net realizable values.

Long-lived assets

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

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." The equity method of accounting requires us 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 continued to recognize losses in excess of our net investment in Regulus up to the principal plus accrued interest we guaranteed, which was $5.6 million at June 30, 2012. Because our share of Regulus' net loss exceeded the $5.6 million we guaranteed, in the second quarter of 2012 we suspended recording our portion of Regulus' net loss. As of June 30, 2012, we had $1.1 million of suspended net losses, which we have not recognized.

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.

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 net loss for the three and six months ended June 30, 2012 and 2011, we did not include the following diluted common equivalent shares in the computation of diluted net loss per share because the effect would have been anti-dilutive:

- $2^5/_8$ percent convertible subordinated notes;
- GlaxoSmithKline convertible promissory notes;
- Dilutive stock options;
- Restricted stock units; and
- Warrants issued to Symphony GenIsis Holdings LLC.

In April 2011, Symphony GenIsis Holdings LLC exercised the remaining warrants.

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 June 30, 2012 and December 31, 2011, we had collaborative arrangements with six entities that we considered 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 the 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 income (loss)

We report the components of comprehensive income (loss) in our condensed consolidated statements of comprehensive income (loss) in the period in which we recognize them. The components of comprehensive income (loss) include net loss and unrealized gains and losses on investment holdings.

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 this debt discount over the life of the debt as additional non-cash interest expense utilizing the effective interest method.

Segment information

We operate in a single segment, Drug Discovery and Development operations, because our chief decision maker reviews operating results on an aggregate basis and manages our operations as a single operating segment.

Stock-based compensation expense

We measure stock-based compensation expense for equity-classified awards, principally related to stock options, restricted stock units, or RSUs, and stock purchase rights under the Employee Stock Purchase Plan, or ESPP, at the grant date, based on the estimated fair value of the award and we recognize the expense over the employee's requisite service period.

We use the Black-Scholes model to estimate the fair value of stock options granted and stock purchase rights under the ESPP. The expected term of stock options granted represents the period of time that we expect them to be outstanding. We estimated the expected term of options granted based on historical exercise patterns. For the six months ended June 30, 2012 and 2011, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Six Months Ended June 30,	
	2012	2011
Risk-free interest rate	0.8%	2.3%
Dividend yield	0.0%	0.0%
Volatility	51.1%	51.4%
Expected Life	5.1 years	5.3 years

ESPP:

	Six Months Ended June 30,	
	2012	2011
Risk-free interest rate	0.1%	0.2%

Dividend yield	0.0%	0.0%
Volatility	42.3%	26.5%
Expected Life	6 months	6 months

In January 2012, we began granting RSUs to our employees. The fair value of RSUs is based on the market price of our common stock on the date of grant. The weighted-average grant date fair value of RSUs granted to employees for the six months ended June 30, 2012 was $7.60 per RSU.

The following table summarizes stock-based compensation expense for the three and six months ended June 30, 2012 and 2011 (in thousands), which was allocated as follows:

	Three Months Ended June 30,		Six Months Ended June 30,	
	2012	2011	2012	2011
Research and development	$ 2,073	$ 2,284	$ 4,008	$ 4,572
General and administrative	387	216	719	660
Total	$ 2,460	$ 2,500	$ 4,727	$ 5,232

As of June 30, 2012, total unrecognized estimated non-cash stock-based compensation expense related to non-vested stock options and RSUs was $8.3 million and $1.1 million, respectively. We will adjust total unrecognized compensation cost for future changes in estimated forfeitures. We expect to recognize the cost of non-cash, stock-based compensation expense related to non-vested stock options and RSUs over a weighted average amortization period of 1.3 years and 3.6 years, respectively.

Impact of recently issued accounting standards

In May 2011, the FASB amended its authoritative guidance on the measurement and disclosure for fair value measurements. The amendment clarifies the application of certain existing fair value measurement guidance and expands the disclosures for fair value measurements that are estimated using significant unobservable (Level 3) inputs. The guidance is effective prospectively for fiscal years, and interim periods within those years, beginning after December 15, 2011 and was effective for our fiscal year beginning January 1, 2012. The adoption of this guidance did not have a material impact on our financial statements.

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 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 companies must report in other comprehensive income or when companies must reclassify an item of other comprehensive income to net income. The guidance is effective retrospectively for fiscal years, and interim periods within those years, beginning after December 15, 2011 and was effective for our fiscal year beginning January 1, 2012. As this guidance relates to presentation only, the adoption of this guidance did not have any other effect on our financial statements.

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3. Investments

As of June 30, 2012, we primarily invested our excess cash in commercial paper and debt instruments of the U.S. Treasury, financial institutions, corporations, and U.S. government agencies with strong credit ratings and 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 June 30, 2012:

One year or less	66%
After one year but within two years	24%
After two years but within three years	10%
Total	100%

As illustrated above, we primarily invest our excess cash in short-term instruments with 90 percent of our available-for-sale securities having a maturity of less than two years.

At June 30, 2012, we had an ownership interest of less than 20 percent in each of three private companies and two public companies with which we conduct business. The companies are Santaris Pharma A/S (formerly Pantheco A/S), Achaogen Inc., and Atlantic Pharmaceuticals Limited, which are privately-held and Antisense Therapeutics Limited, or ATL, and iCo Therapeutics Inc., or iCo, 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.

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

June 30, 2012	Amortized Cost	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Short-term investments:					
Corporate debt securities	$ 115,609	$ 62	$ (45)	$ —	$ 115,626
Debt securities issued by U.S. government agencies	38,564	16	(3)	—	38,577
Debt securities issued by states of the United States and political subdivisions of the states	11,930	6	(3)	—	11,933

Total securities with a maturity of one year or less	166,103	84	(51)	—	166,136
Corporate debt securities	49,671	32	(189)	—	49,514
Debt securities issued by U.S. government agencies	13,660	22	(107)	—	13,575
Debt securities issued by the U.S. Treasury	8,484	9	(3)	—	8,490
Debt securities issued by states of the United States and political subdivisions of the states	12,636	42	(9)	—	12,669
Total securities with a maturity of more than one year	84,451	105	(308)	—	84,248
Subtotal	$ 250,554	$ 189	$ (359)	$ —	$ 250,384
Equity securities:					
Current portion (included in Other current assets)	$ 1,538	$ 1,943	$ —	$ (880)	$ 2,601
Long-term portion (included in Deposits and other assets)	625	—	—	—	625
Subtotal	$ 2,163	$ 1,943	$ —	$ (880)	$ 3,226
	$ 252,717	$ 2,132	$ (359)	$ (880)	$ 253,610

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December 31, 2011	Amortized Cost	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Short-term investments:					
Corporate debt securities	$ 109,842	$ 13	$ (255)	$ —	$ 109,600
Debt securities issued by U.S. government agencies	53,723	35	(5)	—	53,753
Debt securities issued by the U.S. Treasury	2,353	3	—	—	2,356
Debt securities issued by states of the United States and political subdivisions of the states	16,141	4	(3)	—	16,142
Total securities with a maturity of one year or less	182,059	55	(263)	—	181,851
Corporate debt securities	57,632	21	(331)	—	57,322
Debt securities issued by U.S. government agencies	26,754	—	(67)	—	26,687
Debt securities issued by states of the United States and political subdivisions of the states	12,331	19	(23)	—	12,327
Total securities with a maturity of more than one year	96,717	40	(421)	—	96,336
Subtotal	$ 278,776	$ 95	$ (684)	$ —	$ 278,187
Equity securities:					
Current portion (included in Other current assets)	$ 1,538	$ 624	$ —	$ (880)	$ 1,282
Long-term portion (included in Deposits and other assets)	625	—	—	—	625
Subtotal	$ 2,163	$ 624	$ —	$ (880)	$ 1,907
	$ 280,939	$ 719	$ (684)	$ (880)	$ 280,094

Investments we considered to be temporarily impaired at June 30, 2012 were as follows (in thousands):

		Less than 12 months of temporary impairment	
	Number of Investments	Estimated Fair Value	Unrealized Losses
Corporate debt securities	37	$ 80,812	$ (234)
Debt securities issued by U.S. government agencies	6	14,572	(110)
Debt securities issued by the U.S. Treasury	3	5,333	(3)
Debt securities issued by states of the United States and political subdivisions of the states	2	6,548	(12)
Total temporarily impaired securities	48	$ 107,265	$ (359)

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 for identical assets, 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. The majority of our securities have been classified as Level 2. 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. We validate the fair value of securities from our pricing provider by understanding the pricing model they used and comparing their assessment of the fair value

of our Level 2 investments to the fair value provided by the custodians of our Level 2 investments. Our pricing provider and custodians use similar techniques to derive fair value for Level 2 securities. During the three and six months ended June 30, 2012 and 2011 there were no transfers between our Level 1 and Level 2 investments. We use the end of reporting period method for determining transfers between levels. At June 30, 2012 and December 31, 2011, we had no securities that we classified as Level 3.

We measure the following major security types at fair value on a recurring basis. We break down the inputs used to measure fair value for these assets at June 30, 2012 and December 31, 2011 as follows (in thousands):

	At June 30, 2012	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 77,126	$ 77,126	$ —	$ —
Corporate debt securities (2)	165,140	—	165,140	—
Debt securities issued by U.S. government agencies (2)	52,152	—	52,152	—
Debt securities issued by the U.S. Treasury (2)	8,490	8,490	—	—
Debt securities issued by states of the United States and political subdivisions of the states (2)	24,602	—	24,602	—
Equity securities (3)	2,601	2,601	—	—
Total	$ 330,111	$ 88,217	$ 241,894	$ —

	At December 31, 2011	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 58,892	$ 55,893	$ 2,999	$ —
Corporate debt securities (2)	166,922	—	166,922	—
Debt securities issued by U.S. government agencies (2)	80,440	—	80,440	—
Debt securities issued by the U.S. Treasury (2)	2,356	2,356	—	—
Debt securities issued by states of the United States and political subdivisions of the states (2)	28,469	—	28,469	—
Equity securities (3)	1,282	1,282	—	—
Total	$ 338,361	$ 59,531	$ 278,830	$ —

(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.

Other Fair Value Disclosures

Our $2^5/_8$ percent convertible notes had a fair value of $165.3 million and $151.1 million at June 30, 2012 and December 31, 2011, respectively. We determine the fair value of our $2^5/_8$ percent convertible notes based on quoted market prices for these notes which is a Level 2 measurement.

5. Long-Term Obligations

Equipment Financing Arrangement

In October 2008, we entered into a loan agreement related to an equipment financing and in September 2009 and June 2012, we amended the loan agreement to increase the aggregate maximum amount of principal we could draw under the agreement. Each draw down under the loan agreement has a term of three years, with principal and interest payable monthly. Interest on amounts we borrow under the loan agreement is based upon the three year interest rate swap at the time we make each draw down plus 3.5 or four percent, depending on the date of the draw. We are using the equipment purchased under the loan agreement as collateral. In June 2012, we drew down $9.1 million in principal under the loan agreement at an interest rate of 4.12 percent. As of June 30, 2012, we had drawn down $27.4 million in principal under this loan agreement at a weighted average interest rate of 5.51 percent and we can borrow up to an additional $6.0 million in principal to finance the purchase of equipment until April 2014. The carrying balance under this loan agreement at June 30, 2012 and December 31, 2011 was $12.6 million and $5.3 million, respectively. We will continue to use equipment lease financing as long as the terms remain commercially attractive.

6. 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 June 30,		Six Months Ended June 30,	
	2012	2011	2012	2011
Partner A	90%	67%	84%	72%
Partner B	4%	28%	6%	19%

Contract receivables from one significant partner comprised approximately 78 percent of our contract receivables at June 30, 2012. Contract receivables from one significant partner comprised approximately 85 percent of our contract receivables at December 31, 2011.

7. Collaborative Arrangements and Licensing Agreements

Traditional Pharmaceutical Alliances and Licensing

Biogen Idec

In January 2012, we entered into a global collaboration agreement with Biogen Idec valued at up to $299 million to develop and commercialize ISIS-SMN$_{Rx}$ for the treatment of SMA. Under the terms of the agreement, we received an upfront payment of $29 million and are eligible to receive up to $45 million in substantive milestone payments associated with the clinical development of ISIS-SMN$_{Rx}$ prior to licensing. We are responsible for global development of ISIS-SMN$_{Rx}$ through the completion of Phase 2/3 registrational clinical trials. Biogen Idec has the option to license ISIS-SMN$_{Rx}$ through completion of the first successful Phase 2/3 trial. If Biogen Idec exercises its option, it will pay us a license fee and will assume global development, regulatory and commercialization responsibilities. We may also receive up to $150 million in substantive milestone payments if Biogen Idec achieves pre-specified regulatory milestones. We will earn the next milestone payment of $18 million if we initiate the first Phase 2/3 study for ISIS-SMN$_{Rx}$. In addition, we will receive up to double-digit royalties on sales of ISIS-SMN$_{Rx}$ if Biogen Idec successfully develops and commercializes ISIS-SMN$_{Rx}$ after option exercise.

In June 2012, we and Biogen Idec entered into a separate collaboration and license agreement valued at up to $271 million to develop and commercialize a novel antisense drug targeting DMPK for the treatment of myotonic dystrophy type 1, or DM1. Under the terms of the agreement, in July 2012 we received an upfront payment of $12 million and are eligible to receive up to $59 million in substantive milestone payments associated with the development of the DMPK-targeting drug prior to licensing. We are responsible for global development of the drug through the completion of Phase 2 clinical trials. Biogen Idec has the option to license the drug through the completion of the Phase 2 trial. We may also receive up to $130 million in substantive milestone payments if Biogen Idec achieves pre-specified regulatory milestones. In addition, we will receive up to double-digit royalties on future product sales of the drug. We will earn the next milestone payment of $10 million if we initiate an IND-enabling toxicology study for our DMPK program.

During the three and six months ended June 30, 2012, we earned revenue of $1.8 million and $3.6 million, respectively, from our relationship with Biogen Idec which represented four percent and five percent, respectively, of our total revenue for those periods. Our balance sheet at June 30, 2012 included deferred revenue of $25.4 million related to the upfront 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 KYNAMRO™ 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 KYNAMRO™, including the key product related patents, and their foreign equivalents pending or granted in various countries outside the United States, including in the European Union via the European Patent Convention, Japan, Canada, Australia, South Africa and India. In addition, we agreed that we would not develop or commercialize another oligonucleotide-based compound designed to modulate apolipoprotein-B, or apo-B, by binding to the mRNA encoding apo-B, throughout the world.

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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, and a share of worldwide profits on KYNAMRO™ and follow-on drugs ranging from 30 percent to 50 percent of all commercial sales. In May 2012, we earned a $25 million milestone payment from Genzyme when the FDA accepted the NDA for KYNAMRO™. We may also receive over $1.5 billion in substantive milestone payments if Genzyme achieves pre-specified events, including up to $725 million for the achievement of regulatory milestones and up to $825 million for the achievement of commercialization milestones. The next milestone payment we could earn under our agreement with Genzyme is $25 million if the FDA approves the NDA for KYNAMRO™.

Under this alliance, Genzyme is responsible for the continued development and commercialization of KYNAMRO™. We agreed to supply the drug substance for KYNAMRO™ for the Phase 3 clinical trials and initial commercial launch. Genzyme is responsible for manufacturing the finished drug product for KYNAMRO™, including the initial commercial launch supply, and, if approved, Genzyme will be responsible for the long term supply of KYNAMRO™ drug substance and finished drug product. As part of the agreement, we contributed the first $125 million in funding for the development costs of KYNAMRO™, and now we and Genzyme share development costs equally.

The license and co-development agreement for KYNAMRO™ will continue in perpetuity unless we or Genzyme terminate it earlier 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 KYNAMRO™ 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 KYNAMRO™ 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 KYNAMRO™, then the rights to KYNAMRO™ will revert back to us and we may develop and commercialize KYNAMRO™ 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 KYNAMRO™ 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 to monthly limits on the number of shares it can sell of the Company's stock that it purchased in February 2008. In addition, Genzyme has agreed that until the earlier of the 10 year anniversary of the KYNAMRO™ 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 then fair value of our common stock. In May 2012, we finished amortizing this $100 million premium along with the $175 million licensing fee that we received in the second quarter of 2008. During the three and six months ended June 30, 2012, we recognized revenue of $42.8 million and $59.1 million, respectively, primarily related to the upfront payments we received from Genzyme, which represented 90 percent and 84 percent, respectively, of our total revenue for those periods compared to $16.6 million and $33.2 million for the same periods in 2011. Our balance sheets at June 30, 2012 and December 31, 2011 included deferred revenue of $7.5 million and $27.7 million, respectively.

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. Eli Lilly and Company has decided not to continue the development of LY2181308. Therefore we will not earn future milestone payments from Eli Lilly and Company associated with LY2181308.

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Satellite Company Collaborations

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 physicians associate a wide variety of conditions including infection, cancer and chronic inflammation with AI. 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.

In May 2012, Xenon selected XEN701, a drug targeting the hepcidin-hemojuvelin pathway, as a development candidate. Xenon may take an exclusive license for the development and worldwide commercialization of XEN701. Under our collaboration agreement with Xenon we may receive up to $296 million in substantive milestone payments for multiple indications upon the achievement of pre-specified events, including up to $26 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 $3 million if Xenon initiates a phase 2 clinical trial for XEN701. During the three and six months ended June 30, 2012 and 2011, we did not earn any revenue from our relationship with Xenon.

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

In this Report on Form 10-Q, unless the context requires otherwise, "Isis," "Company," "we," "our," and "us," means Isis Pharmaceuticals, Inc. and its subsidiaries, including Regulus Therapeutics Inc., our 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 KYNAMRO™, 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 its 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, 2011, 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 26 of this Report.

Overview

We are the leading company in antisense drug discovery and development, exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs. Antisense technology provides a direct route from genomics to drugs. With our highly efficient and prolific drug discovery platform we can expand our pipeline and our partners' pipelines with antisense drugs that address significant medical needs. Our strategy is to do what we do best—to discover unique antisense drugs and develop these drugs to key clinical value inflection points. We discover and conduct early development of new drugs and, at the key clinical value inflection points, outlicense our drugs to partners. We maximize the value of the drugs we discover by putting them in the hands of leading pharmaceutical companies with late-stage development, commercialization and marketing expertise, such as Biogen Idec, Genzyme, a Sanofi company, and GlaxoSmithKline, or GSK. For instance, our partner, Genzyme, plans to commercialize our lead product, KYNAMRO™, following planned regulatory approval in Europe and in the United States. We also work with a consortium of smaller companies that can exploit our drugs and technologies in areas that are outside of our core focus. As a result of our unique strategy, we can keep our organization small and focused. Our strong financial position is a result of the successful execution of our business strategy as well as our inventive and focused research and development capabilities.

Our flagship product, KYNAMRO™ (formerly mipomersen), is moving closer to the market for patients with severe forms of familial hypercholesterolemia, or FH, at high cardiovascular risk, who cannot reduce their low-density lipoprotein cholesterol, or LDL-C, sufficiently with currently available lipid-lowering therapies. In July 2011, Genzyme submitted a marketing application in Europe for KYNAMRO™ for patients with homozygous familial hypercholesterolemia, or hoFH, and severe heterozygous familial hypercholesterolemia, or severe heFH. In May 2012, the U.S. Food and Drug Administration, or FDA, accepted the marketing application for KYNAMRO™ for patients with hoFH. Genzyme is actively preparing to launch KYNAMRO™ subject to marketing approval. Genzyme is also preparing to commercialize KYNAMRO™ in other major markets.

To maximize the value of our drugs and technologies, we have a multifaceted partnering strategy. We form traditional partnering alliances that enable us to discover and conduct early development of new drugs, outlicense our drugs to partners, such as Genzyme, and build a broad base of license fees, milestone payments and royalty income. We also form preferred partner transactions that provide us with a vested partner, such as Biogen Idec and GSK, early in the development of a drug. In this way, we benefit in the short term from upfront option fees and development milestone payments while we maintain control over the early development of the drug. We benefit in the long term by having a knowledgeable and committed partner to license the drug at clinical proof-of-concept and by receiving regulatory milestone payments and royalties as our partner moves the drug to the market. In all of our partnerships, we benefit from the expertise our partners bring to our drugs. We also work with a consortium of smaller companies that can exploit our drugs and technologies. We call these smaller companies our satellite companies. In this way, we benefit from the disease-specific expertise of our satellite company partners, who are advancing drugs in our pipeline in areas that are outside of our core focus. In addition, we can maintain our broad RNA technology leadership through collaborations with companies such as Alnylam Pharmaceuticals, Inc., or Alnylam, and Regulus Therapeutics Inc., or Regulus, a company we jointly own focused on microRNA therapeutics. All of these different types of relationships are part of our unique business model and create near and long-term shareholder value.

The clinical successes of the drugs in our pipeline continue to create new partnering opportunities. For example, in January 2012, we formed a strategic alliance with Biogen Idec to develop and commercialize ISIS-SMN$_{Rx}$ to treat spinal muscular atrophy. We received a $29 million upfront payment and are eligible to receive up to $270 million in payments as well as double-digit royalties on sales from ISIS-SMN$_{Rx}$. Since 2007, our partnerships have generated an aggregate of more than $875 million in payments from upfront and licensing fees, equity purchase payments, milestone payments and research and development funding, including the $12 million upfront payment we received from Biogen Idec in July 2012 related to our new alliance valued at up to $271 million to develop and commercialize a drug targeting dystrophia myotonica-protein kinase, or DMPK. In addition, for our current partnered programs we have the potential to earn $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, or royalty arrangements. Our strong financial position is a result of the successful execution of our business strategy as well as our inventive and focused research and development capabilities.

We protect our proprietary technologies and products through our substantial patent estate. As an innovator in RNA-targeting 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, we continue to add to our substantial patent estate. 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 $400 million from our intellectual property sale and licensing program that helps support our internal drug discovery and development programs.

Recent Events

Drug Development and Corporate Highlights

- KYNAMRO™ continues to advance in development and move closer to the market for patients with severe forms of familial hypercholesterolemia (FH; homozygous FH and severe heterozygous FH), at high cardiovascular risk, who cannot reduce their LDL-C sufficiently with currently available lipid-lowering therapies.
    - The FDA accepted for filing the NDA for KYNAMRO™ for the treatment of patients with homozygous FH.
    - We received a $25 million milestone payment from Genzyme for the KYNAMRO™ NDA filing.
    - A clinical investigator presented an analysis of lipoprotein a, or Lp(a), data from the KYNAMRO™ Phase 3 program at the European Atherosclerosis Society. The data demonstrated sustained reductions of Lp(a), an independent risk factor for cardiovascular disease.
- We received European GMP certification of our manufacturing facility for production of drug substance to support KYNAMRO™ commercial launch.
- We initiated a Phase 2 study evaluating ISIS-APOCIII$_{Rx}$ in patients with hypertriglyceridemia, a condition characterized by high levels of triglycerides that is often associated with premature coronary artery disease and pancreatitis.

- We formed a new strategic alliance with Biogen Idec to develop and commercialize a drug to treat DM1 that expands our severe and rare disease franchise. We received a $12 million upfront payment and are eligible to receive up to an additional $259 million in a licensing fee and milestone payments. We will also receive double-digit royalties on product sales.
- We and collaborators published a paper in Nature demonstrating that an antisense compound selectively and rapidly reduced target RNA in skeletal muscle and alleviated disease in animal models of DM1.
- We and collaborators published a paper in Neuron demonstrating that an antisense compound reversed disease in animal models of Huntington's disease.
- We received Orphan Drug Designation in the United States for ISIS-TTR$_{Rx}$ for the treatment of TTR amyloidosis.

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

- 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.

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, 2011.

Results of Operations

Revenue

Total revenue for the three and six months ended June 30, 2012 was $47.3 million and $70.6 million, respectively, compared to $24.8 million and $46.0 million for the same periods in 2011. Our revenue fluctuates based on the nature and timing of payments under agreements with our partners, including license fees, milestone-related payments and other payments. For example, our revenue in the first half of 2012 was significantly higher than in the first half of 2011 primarily due to the $25 million milestone payment we earned from Genzyme for the FDA acceptance of the KYNAMRO™ NDA. Also in the first half of 2012, we sold $6.2 million of drug substance to Genzyme to support the planned commercial launch of KYNAMRO™ and began recognizing revenue from the $29 million upfront payment we received from Biogen Idec earlier this year. These increases were partially offset by $5.5 million less in revenue because amortization of the upfront payments associated with the Genzyme collaboration ended in May 2012.

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As mentioned above, our revenue fluctuates from quarter to quarter based on the timing of payments from our partners as the Genzyme $25 million milestone payment we earned in the second quarter of this year clearly demonstrates. Also, we earned $27.7 million from the amortization of the Genzyme upfront payments, which ended as anticipated in the May of 2012. As a result, that will not be a component of revenue in the second half of 2012.

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for the three and six months ended June 30, 2012 was $47.1 million and $69.0 million, respectively, compared to $24.3 million and $44.3 million for the same periods in 2011. The increase in the first half of 2012 was primarily due to the $25 million milestone payment and $6.2 million in sales of drug substance that we earned from Genzyme and revenue we earned from our partner, Biogen Idec, partially offset by a decrease in revenue when the amortization of the upfront payments associated with the Genzyme collaboration ended in May 2012.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties for the three and six months ended June 30, 2012 was $200,000 and $1.6 million, respectively, and was essentially flat when compared to $518,000 and $1.7 million for the same periods in 2011.

Operating Expenses

Operating expenses for the three and six months ended June 30, 2012 were $43.6 million and $85.3 million, respectively, compared to $38.9 million and $76.1 million for the same periods in 2011. The moderately higher expenses in the first half of 2012 were primarily due to higher development costs associated with our maturing pipeline of drugs offset by lower development expenses related to KYNAMRO™ because Genzyme is now sharing these expenses equally with us until KYNAMRO™ is profitable. In addition, Genzyme is paying all of the marketing and selling expenses until KYNAMRO™ is profitable.

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 equity awards from our operating expenses. We believe non-cash compensation expense is not indicative of our operating results or cash flows from our operations. Further, we internally evaluate the performance of our operations excluding it.

Research and Development Expenses

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

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2012	2011	2012	2011
Research and development expenses	$ 38,362	$ 33,725	$ 75,141	$ 65,682
Non-cash compensation expense related to equity awards	2,073	2,284	4,008	4,572
Total research and development	$ 40,435	$ 36,009	$ 79,149	$ 70,254

For the three and six months ended June 30, 2012, we incurred total research and development expenses of $38.4 million and $75.1 million, respectively, compared to $33.7 million and $65.7 million for the same periods in 2011. The higher expenses in the first half of 2012 were primarily due to higher development costs associated with our maturing pipeline of drugs offset, in part, by lower development expenses related to KYNAMRO™. As drugs move forward to more advanced stages of development, including into larger, longer clinical studies, the costs of development increase. All amounts exclude non-cash compensation expense related to equity awards.

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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 June 30,		Six Months Ended June 30,	
	2012	2011	2012	2011
Antisense drug discovery	$ 8,429	$ 8,019	$ 16,793	$ 15,200
Non-cash compensation expense related to equity awards	600	671	1,165	1,313
Total antisense drug discovery	$ 9,029	$ 8,690	$ 17,958	$ 16,513

Antisense drug discovery costs for the three and six months ended June 30, 2012 were $8.4 million and $16.8 million, respectively, compared to $8.0 million and $15.2 million for the same periods in 2011. The higher expenses in the first half of 2012 compared to the same period in 2011 were primarily due to increased research services provided by third parties to support our partnered research programs. All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Development

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2012	2011	2012	2011
KYNAMRO™	$ 2,431	$ 2,433	$ 5,466	$ 5,976
Other antisense development products	14,496	10,742	26,693	19,297
Development overhead costs	1,549	1,498	3,450	3,109
Non-cash compensation expense related to equity awards	724	747	1,381	1,520
Total antisense drug development	$ 19,200	$ 15,420	$ 36,990	$ 29,902

Antisense drug development expenditures were $18.5 million and $35.6 million, respectively, for the three and six months ended June 30, 2012, compared to $14.7 million and $28.4 million for the same periods in 2011. The higher expenses in the first half of 2012 were primarily due to an increase in development costs associated with our maturing pipeline of drugs offset, in part, by lower development expenses related to KYNAMRO™. As drugs move forward to more advanced stages of development, including into larger, longer clinical studies, the costs of development increase. All amounts exclude non-cash compensation expense related to equity awards.

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

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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. We have partnered 13 of our 25 drug candidates, which substantially reduces our development costs. As part of our collaboration with Genzyme, we have transitioned the majority of the development responsibility for KYNAMRO™ to Genzyme. In 2011, we satisfied our $125 million development funding obligation. We and Genzyme now share development costs equally. Our shared funding will end when the program is profitable.

Manufacturing and Operations

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

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2012	2011	2012	2011
Manufacturing and operations	$ 5,115	$ 4,734	$ 9,685	$ 9,285
Non-cash compensation expense related to equity awards	302	304	564	611
Total manufacturing and operations	$ 5,417	$ 5,038	$ 10,249	$ 9,896

Manufacturing and operations expenses increased slightly for the three and six months ended June 30, 2012 and 2011 with $5.1 million and $9.7 million, respectively, compared to $4.7 million and $9.3 million for the same periods in 2011. All amounts exclude non-cash compensation expense related to equity awards.

R&D Support

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

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2012	2011	2012	2011
Personnel costs	$ 2,274	$ 2,118	$ 4,541	4,182
Occupancy	1,675	1,862	3,403	3,648
Depreciation and amortization	1,321	1,478	2,460	3,294
Insurance	271	214	581	427
Other	801	627	2,069	1,264
Non-cash compensation expense related to equity awards	447	562	898	1,128
Total R&D support costs	$ 6,789	$ 6,861	$ 13,952	$ 13,942

R&D support costs for the three and six months ended June 30, 2012 were $6.3 million and $13.1 million, respectively, compared to $6.3 million and $12.8 million for the same periods in 2011. Expenses in the first half of 2012 compared to the same period in 2011 are essentially flat. The increase in Other costs primarily relates to litigation costs for our patent infringement lawsuit against Santaris Pharma A/S offset by a reduction in Depreciation and Amortization because of non-cash charges related to patents and patent applications that we wrote off in 2011 because we were no longer pursuing them. All amounts exclude non-cash compensation expense related to equity awards.

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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.

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

	Three Months Ended	Six Months Ended

	June 30,		June 30,	
	2012	2011	2012	2011
General and administrative expenses	$ 2,822	$ 2,658	$ 5,466	$ 5,224
Non-cash compensation expense related to equity awards	387	216	719	660
Total general and administrative expenses	$ 3,209	$ 2,874	$ 6,185	$ 5,884

General and administrative expenses are essentially flat for the three and six months ended June 30, 2012 with $2.8 million and $5.5 million, respectively, compared to $2.7 million and $5.2 million for the same periods in 2011. All amounts exclude non-cash compensation expense related to equity awards.

Equity in Net Loss of Regulus Therapeutics Inc.

Our equity in net loss of Regulus for the three and six months ended June 30, 2012 was $163,000 and $1.1 million, respectively, compared to $1.0 million and $1.9 million for the same periods in 2011. Under the equity method of accounting, we are required to suspend recognizing losses if our share of Regulus' net loss 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 continued to recognize losses in excess of our net investment in Regulus up to the principal plus accrued interest we guaranteed, which was $5.6 million at June 30, 2012. Because our share of Regulus' net loss exceeded the $5.6 million we guaranteed, in the second quarter of 2012 we suspended recording our portion of Regulus' net loss. As of June 30, 2012, we had $1.1 million of suspended net losses, which we have not recognized.

Investment Income

Investment income for the three and six months ended June 30, 2012 was $477,000 and $1.1 million, respectively, compared to $616,000 and $1.3 million for the same periods in 2011. The decrease in investment income was primarily due to a lower average cash balance.

Interest Expense

Interest expense for the three and six months ended June 30, 2012 was $5.2 million and $10.4 million, respectively, compared to $3.4 million and $6.9 million for the same periods in 2011. The increase in interest expense in 2012 is primarily a result of additional non-cash interest expense we recorded for the long-term liability associated with our new facility.

Gain (Loss) on Investments, Net

Net gain on investments for the three and six months ended June 30, 2012 was $2,000 and $19,000, respectively, compared to a net gain of $34,000 for the three months ended June 30, 2011 and a net loss of $285,000 for the six months ended June 30, 2011. The loss on investments for the first six months of 2011 was primarily due to a $359,000 valuation allowance we recorded related to an investment we made in Excaliard Pharmaceuticals, Inc. offset by nominal gains on our available for sale securities.

Net Loss and Net Loss per Share

Net loss for the three and six months ended June 30, 2012 was $1.2 million and $25.2 million, respectively, compared to a net loss of $17.9 million and $37.9 million for the same periods in 2011. Basic and diluted net loss per share for the three and six months ended June 30, 2012 was $0.01 per share and $0.25 per share, respectively, compared to $0.18 per share and $0.38 per share for the same periods in 2011. Our net loss for the first half of 2012 decreased compared to the same period in 2011 primarily due to a decrease in our net operating loss, which is discussed above, partially offset by additional non-cash interest expense we recorded for the long-term liability associated with our new facility.

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Liquidity and Capital Resources

We have financed our operations with revenue primarily from research and development collaborative agreements. Additionally, we have earned revenue from the sale or licensing of our intellectual property. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From our inception through June 30, 2012, we have earned approximately $1.1 billion in revenue from contract research and development and the sale and licensing of our intellectual property. From the time we were founded through June 30, 2012, we have raised net proceeds of approximately $825.4 million from the sale of our equity securities and we have borrowed approximately $577.7 million under long-term debt arrangements to finance a portion of our operations.

As of June 30, 2012, we had cash, cash equivalents and short-term investments of $336.0 million and stockholders' equity of $154.3 million. In comparison, we had cash, cash equivalents and short-term investments of $343.7 million and stockholders' equity of $171.4 million at December 31, 2011. At June 30, 2012, we had consolidated working capital of $295.4 million, compared to $284.0 million at December 31, 2011. The decrease in cash in the first half of 2012 primarily relates to cash used for our operations offset by the $25 million milestone payment we received from Genzyme and the $29 million upfront payment we received from Biogen Idec. Our cash balance at June 30, 2012 does not include the $12 million upfront payment that we received in July 2012 from our new collaboration with Biogen Idec to develop and commercialize a drug to treat DM1.

As of June 30, 2012, our debt and other obligations totaled $231.1 million, compared to $218.8 million at December 31, 2011. The increase was primarily related to $9.1 million of additional draw downs on our equipment financing arrangement and $4.6 million of non-cash amortization of the debt discount we recorded in the first half of 2012, which increased the carrying value of our $2^{5}/_{8}$ percent convertible notes, offset in part by $4.8 million of rent and principal payments we made in the first half of 2012 on our building lease obligation and equipment financing arrangement.

The following table summarizes our contractual obligations as of June 30, 2012. 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:

Contractual Obligations (selected balances described below)	Payments Due by Period (in millions) 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)	$ 168.9	$ 4.3	$ 164.6	$ —	$ —
New Facility Rent Payments	$ 146.7	$ 5.8	$ 12.2	$ 12.9	$ 115.8
Equipment Financing Arrangements (principal and interest payable)	$ 13.3	$ 5.5	$ 7.5	$ 0.3	$ —
Other Obligations (principal and interest payable)	$ 1.4	$ 0.1	$ 0.1	$ 0.1	$ 1.1
Capital Lease	$ 0.6	$ 0.2	$ 0.3	$ 0.1	$ —
Operating Leases	$ 28.2	$ 1.4	$ 2.8	$ 2.7	$ 21.3
Total	$ 359.1	$ 17.3	$ 187.5	$ 16.1	$ 138.2

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 through 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 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 and June 2012, we amended the loan agreement to increase the aggregate maximum amount of principal we could draw under the agreement. Each draw down under the loan agreement has a term of three years, with principal and interest payable monthly. Interest on amounts we borrow under the loan agreement is based upon the three year interest rate swap at the time we make each draw down plus 3.5 or four percent, depending on the date of the draw. We are using the equipment purchased under the loan agreement as collateral. As of June 30, 2012, we had drawn down $27.4 million in principal under this loan agreement at a weighted average interest rate of 5.51 percent and we can borrow up to an additional $6.0 million in principal to finance the purchase of equipment until April 2014. The carrying balance under this loan agreement at June 30, 2012 and December 31, 2011 was $12.6 million and $5.3 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 lease agreement with an affiliate of BioMed Realty, L.P. Under the lease, BioMed 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. The leases on our former primary research and development facilities expired at the end of 2011. Rather than invest in costly renovations to these facilities, we chose to consolidate the majority of our operations in this new leased facility that Biomed constructed. To make our move as efficient as possible, we requested access to the new facility prior to the completion of construction. To gain early access, 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 2011, we consolidated the majority of our operations into the new facility and began depreciating the building over its economic life. Our rent payments, which began 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 June 30, 2012 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 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, 2011.

Risks Associated with our Drug Discovery and Development Business

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

We cannot guarantee that any of our drugs, including KYNAMRO™, 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

KYNAMRO™, before a drug can be approved for sale. We must conduct these studies in compliance with U.S. 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 KYNAMRO™. Even though Genzyme has submitted marketing approval applications for KYNAMRO™ in Europe and the United States, it is possible that regulatory agencies will not approve KYNAMRO™ 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 KYNAMRO™, 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 KYNAMRO™, 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 KYNAMRO™, 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 KYNAMRO™, are safe and effective for human use, we may need to abandon one or more of our drug development programs. We have ongoing clinical studies for KYNAMRO™, adverse events from which could negatively impact our pending marketing approval applications.

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 KYNAMRO™ and in clinical studies for our other drugs. If any of our drugs in clinical studies, including KYNAMRO™, 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 KYNAMRO™ 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 KYNAMRO™. 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 KYNAMRO™, could reduce the commercial potential or viability of our drugs.

Even if approved, KYNAMRO™ 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 KYNAMRO™. The FDA and foreign regulatory authorities have 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 or a foreign regulatory authority 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 or a foreign regulatory authority 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 KYNAMRO™.

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

If KYNAMRO™ 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 authorities approve KYNAMRO™ 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.

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 KYNAMRO™, 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 KYNAMRO™ or our other drugs or increase patient coinsurance to a level that makes KYNAMRO™ or our other drugs unaffordable.

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

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

We entered into this collaboration primarily to:

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

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 KYNAMRO™, 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 KYNAMRO™. Our collaboration with Genzyme may not continue or result in the successful commercialization of KYNAMRO™. Genzyme can terminate our collaboration at any time. If Genzyme stopped developing or commercializing KYNAMRO™, we would have to seek additional sources for funding and may have to delay or reduce our development and commercialization programs for KYNAMRO™. If Genzyme does not successfully commercialize KYNAMRO™, we may receive limited or no revenues for KYNAMRO™. In addition, Sanofi's acquisition of Genzyme could disrupt Genzyme or distract it from performing its obligations under our collaboration.

If Genzyme cannot manufacture finished drug product for KYNAMRO™ or the post-launch supply of the active drug substance for KYNAMRO™, KYNAMRO™ 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 KYNAMRO™, if approved. However, we rely on Genzyme to manufacture the finished drug product for KYNAMRO™, including the initial commercial launch supply. In addition, if approved, Genzyme will be responsible for the long term supply of both KYNAMRO™ drug substance and finished drug product. Genzyme may not be able to reliably manufacture KYNAMRO™ drug substance and drug product to support the long term commercialization of KYNAMRO™. If Genzyme cannot reliably manufacture KYNAMRO™ drug substance and drug product, KYNAMRO™ 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 KYNAMRO™, or result in enforcement action after approval that could limit the commercial success of our drugs, including KYNAMRO™.

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 KYNAMRO™, 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 KYNAMRO™.

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 KYNAMRO™, some competitors are pursuing a development strategy that competes with our strategy for KYNAMRO™. Other companies are currently developing products that could compete with KYNAMRO™. 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 KYNAMRO™. For example, Aegerion has submitted a new drug application to the FDA and a marketing authorization application to the European Medicines Agency seeking approval of its MTP inhibitor, lomitapide, as an adjunct to a low fat diet and other lipid-lowering therapies to reduce cholesterol in patient with HoFH. Our revenues and financial position will suffer if KYNAMRO™ 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 KYNAMRO™. 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 KYNAMRO™.

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 June 30, 2012, we had an accumulated deficit of approximately $866.7 million and stockholders' equity of approximately $154.3 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, Biogen Idec, iCo, Genzyme, GSK, OncoGenex, Pfizer, 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.

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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 Biogen Idec, 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 Biogen Idec, 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;
- 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 KYNAMRO™.

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 KYNAMRO™, the price of our securities would likely decrease.

For example, in April 2008 the FDA provided guidance regarding approval requirements for KYNAMRO™. The FDA indicated that reduction of LDL-C is an acceptable surrogate endpoint for accelerated approval of KYNAMRO™ for use in patients with HoFH. 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 in March 2012 submitted a new drug application (NDA) seeking approval for KYNAMRO™ for the treatment of patients with HoFH in the United States.

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.

From time to time we have to defend our intellectual property rights. In the event of an intellectual property dispute, we sometimes need to litigate to defend our rights or assert them against others. Disputes can 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 June 30, 2012, we had cash, cash equivalents and short-term investments equal to $336.0 million. If we do not meet our goals to commercialize KYNAMRO™ 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 commercial launch of KYNAMRO™;
- 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 terminated 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 June 30, 2012, the market price of our common stock ranged from $6.25 to $12.00 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.

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. We store these materials and various wastes resulting from their use 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. If 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 discovering, developing, and commercializing 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 if our facilities are affected by a disaster, our development and commercialization efforts would be delayed. Although we possess insurance for damage to our property and the disruption of our business from casualties, this insurance may not be sufficient to cover all of our potential losses and may not continue to be available to us on acceptable terms, or at all.

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

Our certificate of incorporation provides for classified terms for the members of our board of directors. Our certificate also includes a provision that requires at least 66 ²¤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.

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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. In addition, our board of directors has the authority to fix the rights and preferences of, and issue shares of preferred stock, which may have the effect of delaying or preventing a change in control of our company without action by our stockholders.

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

In addition, our collaboration agreement with Genzyme regarding KYNAMRO™ provides that if we are acquired, Genzyme may elect to purchase all of our rights to receive payments under the KYNAMRO™ 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.

These provisions, as well as Delaware law, including Section 203 of the Delaware General Corporation 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.

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 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, or where the SEC has adopted, 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 are 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.

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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 primarily invest our excess cash in highly liquid short-term investments of the U.S. Treasury and reputable financial institutions, corporations, and U.S. government agencies with strong credit ratings. We typically hold our investments for the duration of the term of the respective instrument. We do not utilize derivative financial instruments, derivative commodity instruments or other market risk sensitive instruments, positions or transactions to manage exposure to interest rate changes. Accordingly, we believe that, while the securities we hold are subject to changes in the financial standing of the issuer of such securities, we are not subject to any material risks arising from changes in interest rates, foreign currency exchange rates, commodity prices, equity prices or other market changes that affect market risk sensitive instruments.

ITEM 4. CONTROLS AND PROCEDURES

As of the end of the period covered by this Quarterly Report on Form 10-Q, we carried out an evaluation, under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended. Based on this evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of June 30, 2012. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to June 30, 2012.

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. In December 2011, Santaris filed an answer to our complaint, denying our allegations, and seeking a declaration from the court that Santaris has not, and does not, infringe the patents we asserted against Santaris in the suit. In January 2012, Santaris filed a motion for summary judgment asking the court to decide as a matter of law that Santaris' activities do not infringe the patents we assert in the suit.

In January 2012, Alnylam Pharmaceuticals, Inc. filed a patent infringement lawsuit against Tekmira Pharmaceuticals Corporation in the U.S. District Court of the District of Massachusetts. Alnylam's lawsuit alleges Tekmira has infringed a number of issued patents related to siRNA and LNP technologies, including: U.S. Patent No. 7,695,902; U.S. Patent No. 6,858,225; U.S. Patent No. 6,815,432; U.S. Patent No. 6,534,484; U.S. Patent No. 6,586,410; and, U.S. Patent No. 6,858,224. Under Alnylam's contractual right to enforce Isis' patent U.S. Patent No. 7,695,902, Alnylam joined us to the suit as a co-plaintiff.

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

Not applicable

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable

ITEM 5. OTHER INFORMATION

Not applicable

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.1	DMPK Research, Development, Option and License Agreement dated June 27, 2012 between the Registrant and Biogen Idec MA Inc. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.2	Third Amendment to Loan Agreement dated June 27, 2012 between the Registrant and RBS Asset Finance, Inc.
10.3	Form of Restricted Stock Unit Grant Notice and Agreement under Registrant's 2002 Non-Employee Director's Stock Option Plan.
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 Offic5er 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 June 30, 2012, formatted in Extensive Business Reporting Language (XBRL): (i) condensed consolidated balance sheets, (ii) condensed consolidated statements of operations, (iii) condensed consolidated statements of comprehensive loss, (iv) condensed consolidated statements of cash flows and (v) notes to condensed consolidated financial statements (detail tagged).

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)	August 6, 2012
/s/ B. Lynne Parshall B. Lynne Parshall, J.D.	Director, Chief Operating Officer, Chief Financial Officer and Secretary (Principal financial and accounting officer)	August 6, 2012

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

DMPK RESEARCH, DEVELOPMENT, OPTION AND LICENSE AGREEMENT

BETWEEN

ISIS PHARMACEUTICALS, INC.,

AND

BIOGEN IDEC MA INC.

DMPK RESEARCH, DEVELOPMENT, OPTION AND LICENSE AGREEMENT

This DMPK RESEARCH, DEVELOPMENT, OPTION AND LICENSE AGREEMENT (the "***Agreement***") is entered into as of the 27th day of June, 2012 (the "***Effective Date***") by and between **ISIS PHARMACEUTICALS, INC.**, a Delaware corporation, having its principal place of business at 2855 Gazelle Court, Carlsbad, CA 92010 ("***Isis***"), and **BIOGEN IDEC MA INC.**, a Massachusetts corporation, having its principal place of business at 14 Cambridge Center, Cambridge, MA 02142 ("***Biogen Idec***"). Biogen Idec and Isis each may be referred to herein individually as a "***Party***" or collectively as the "***Parties***." Capitalized terms used in this Agreement, whether used in the singular or the plural, have the meaning set forth in APPENDIX 1. All attached appendices and schedules are a part of this Agreement.

RECITALS

WHEREAS, Isis has proprietary technology with respect to antisense therapeutics, and is identifying a drug to treat Myotonic Dystrophy-Type 1;

WHEREAS, Biogen Idec has expertise in developing and commercializing human therapeutics, and Biogen Idec is interested in developing and commercializing an antisense therapeutic for Myotonic Dystrophy-Type 1;

WHEREAS, Biogen Idec desires Isis to (i) identify a Development Candidate for Myotonic Dystrophy-Type 1, (ii) Develop the Development Candidate through completion of the PoC Trial, and (iii) provide Biogen Idec an Option to obtain an exclusive license under this Agreement to Develop, Manufacture and Commercialize Products in the Field.

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

ARTICLE 1.
RESEARCH AND DEVELOPMENT

1.1. **Research and Development Term**. The term for the conduct of the ISIS-DMPK$_{Rx}$ R&D Plan will begin on the Effective Date and will end upon the earlier of (i) completion of the PoC Trial, which the Parties estimate will be approximately [***] years after the Effective Date, or (ii) mutual agreement of the Parties.

1.2. **Development Management**.

1.2.1. **JSC**. The Parties will establish a joint steering committee (the "***JSC***") to provide advice and make recommendations on the conduct of activities under the ISIS-DMPK$_{Rx}$ R&D Plan, which advice and recommendations will be consistent with the ISIS-DMPK$_{Rx}$ R&D Plan. The JSC will consist of two representatives appointed by Isis and two representatives appointed by Biogen Idec. Each JSC member will be a senior development staff leader or have similar experience and expertise as a senior development staff leader. Each Party will designate one of its

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two representatives who is empowered by such Party to make decisions related to the performance of such Party's obligations under this Agreement to act as the co-chair of the JSC. The co-chairs will be responsible for overseeing the activities of the JSC consistent with the responsibilities set forth in Section 1.2.2. SCHEDULE 1.2.1 sets forth certain JSC governance matters agreed to as of the Effective Date. The JSC will determine the JSC operating procedures at its first meeting, including the JSC's policies for replacement of JSC members, policies for participation by additional representatives or consultants invited to attend JSC meetings, and the location of meetings, which will be codified in the written minutes of the first JSC meeting. Each Party will be responsible for the costs and expenses of its own employees or consultants attending JSC meetings. Isis and Biogen Idec will use reasonable efforts to schedule meetings of the JSC to take place at the same location and on the same dates as meetings of the JDC under the Development, Option and License Agreement between the Parties dated January 3, 2012 (the "***SMN Agreement***"), to maximize the use of each Party's time, increase information sharing efficiencies and reduce the cost of additional travel, lodging and related expenses.

1.2.2. **Role of the JSC**. Without limiting any of the foregoing, subject to Section 1.2.3, the JSC will perform the following functions, some or all of which may be addressed directly at any given JSC meeting:

(a) review the overall progress of Isis' efforts to discover, identify, optimize and select the Development Candidate under the ISIS-DMPK$_{Rx}$ R&D Plan;

(b) review and provide advice on the ISIS-DMPK$_{Rx}$ R&D Plan, including whether and how to conduct any of the activities listed on SCHEDULE 1.2.2(b);

(c) amend the ISIS-DMPK$_{Rx}$ R&D Plan upon unanimous written consent;

(d) review and provide advice on the Phase 1 Trial Design and the PoC Trial Design; and

(e) such other review and advisory responsibilities as may be assigned to the JSC pursuant to this Agreement.

1.2.3. **Decision Making**. Isis will conduct the ISIS-DMPK$_{Rx}$ R&D Plan giving due consideration to the recommendations and advice of the JSC. Subject to Section 1.3.1, prior to Option exercise, Isis will have the final decision-making authority regarding [***], and [***]. After Option exercise, Biogen Idec will have the final decision-making authority regarding the Manufacture, Development and Commercialization of Products. Except as otherwise permitted by Section 1.2.2(c), the JSC will have no decision making authority and will act as a forum for sharing information about the activities conducted by the Parties hereunder and as an advisory body, in each case only on the matters described in, and to the extent set forth in, this Agreement.

1.2.4. **Term of the JSC**. Isis' obligation to participate in the JSC will terminate upon Biogen Idec's exercise of the Option. Thereafter, Isis will have the right, but not the obligation, to participate in JSC meetings upon Isis' request.

1.2.5. **Briefing the JSC**. At each regularly scheduled meeting of the JSC prior to exercise of the Option, Isis will provide to the JSC a progress update on Research and Development activities under the ISIS-DMPK$_{Rx}$ R&D Plan.

1.2.6. **Alliance Managers**. Each Party will appoint a representative to act as its alliance manager (each, an "***Alliance Manager***"). Each Alliance Manager will be responsible for supporting the JSC and performing the activities listed in SCHEDULE 1.2.6.

1.3. **Isis' Research and Development Responsibilities**.

1.3.1. **ISIS-DMPK$_{Rx}$ R&D Plan**. Isis will carry out its Research and Development efforts for the Development Candidate pursuant to the ISIS-DMPK$_{Rx}$ R&D Plan. Isis will, subject to the provisions of this Agreement, update the ISIS-DMPK$_{Rx}$ R&D Plan with any non-material changes as needed, but at least once Annually, and submit it to the JSC for its review and comment. Any material changes to the ISIS-DMPK$_{Rx}$ R&D Plan, including any material changes to the Phase 1 Trial Design or the PoC Trial Design, must be unanimously agreed to by the JSC. Without limiting any of the foregoing, [***] in the ISIS-DMPK$_{Rx}$ R&D Plan is deemed to be a material change to the ISIS-DMPK$_{Rx}$ R&D Plan that must be unanimously agreed to by the JSC.

1.3.2. **Development Candidate**. Isis will notify Biogen Idec in writing within 30 days of designating a Development Candidate and will provide Biogen Idec the applicable Development Candidate Data Package.

1.3.3. **Drug Development**. Isis will use Commercially Reasonable Efforts to conduct all activities under the ISIS-DMPK$_{Rx}$ R&D Plan on the timeline set forth in the ISIS-DMPK$_{Rx}$ R&D Plan, including the following Development activities under this Agreement:

(a) Subject to Section 1.4 below, Develop the Development Candidate through the completion of the PoC Trial; *provided, however,* Isis may discontinue such Development if at any time after having consulted, and having given good faith consideration to the recommendations of the JSC and a mutually-agreed Third Party expert, Isis in good faith believes that continuing such Development would (i) pose an unacceptable risk or threat of harm in humans, or (ii) violate any Applicable Law, ethical principles, or principles of scientific integrity. Prior to discontinuing Development of the Development Candidate, Isis will provide Biogen

Idec with reasonable advance notice of such discontinuation, including the grounds for Isis' determination. If Isis elects to discontinue Development of the Development Candidate pursuant to this Section 1.3.3(a), Biogen Idec may, in its discretion, elect to continue Development of the Development Candidate by providing Isis with written notice of Biogen Idec's exercise of the Option within 90 days after Isis' written notice to Biogen Idec of such discontinuation. If Biogen Idec timely executes its Option under this Section 1.3.3(a), then [***]. If Biogen Idec does not timely execute its Option under this Section 1.3.3(a), then the Option will expire.

(b) ***Phase 1 Trials***. Each Phase 1 Trial will be designed in accordance with the applicable Phase 1 Trial Design set forth in the ISIS-DMPK$_{Rx}$ R&D Plan. Isis will keep Biogen Idec informed of the progress and status of each Phase 1 Trial. When Isis completes a Phase 1 Trial, Isis will notify Biogen Idec in writing within 30 days. Isis will provide Biogen Idec with the data generated under the [***] for such Phase 1 Trial as soon as practicable after such notice.

(c) ***PoC Trial***. The PoC Trial will be designed in accordance with the PoC Trial Design set forth in the ISIS-DMPK$_{Rx}$ R&D Plan. Isis will keep Biogen Idec informed of the progress and status of the PoC Trial. When Isis completes the PoC Trial under the ISIS-DMPK$_{Rx}$ R&D Plan, Isis will notify Biogen Idec in writing within 30 days after such completion. Isis will provide Biogen Idec with [***] as soon as practicable after such notice. If Biogen Idec exercises the Option prior to the Initiation of the PoC Trial, Biogen Idec will keep Isis informed of the progress and status of the PoC Trial. When Biogen Idec completes the PoC

Trial, Biogen Idec will notify Isis in writing within 30 days after such completion, and will provide Isis with [***] as soon as practicable after such notice.

1.3.4. **Conduct of Research and Development**. Isis will conduct its work under the ISIS-DMPK$_{Rx}$ R&D Plan in a good scientific manner, and in compliance with all applicable good laboratory practices and cGMP, and all Applicable Laws.

1.4. **Research and Development Costs and Expenses**.

1.4.1. **Research and Development Costs Paid by Isis**. Until Biogen Idec exercises the Option, Isis will be responsible for all research and Development activities for the Development Candidate under the ISIS-DMPK$_{Rx}$ R&D Plan and, except as otherwise provided under Section 1.4.2, all costs and expenses associated therewith.

1.4.2. **Development Costs Paid by Biogen Idec**.

(a) **Before Option Exercise**. Biogen Idec will be responsible for paying any Additional R&D Plan Costs resulting from Biogen-Initiated Changes. Isis will permit Biogen Idec to review, negotiate (with Isis) and approve the Additional R&D Plan Costs before implementing any Biogen-Initiated Changes. Isis and Biogen Idec will update the ISIS-DMPK$_{Rx}$ R&D Plan with any such revised studies and Isis will invoice Biogen Idec for any such approved Additional R&D Plan Costs. Biogen Idec will pay the invoices submitted pursuant to this Section 1.4.2(a) for such approved Additional R&D Plan Costs within 45 days after receipt of the applicable invoice by Biogen Idec.

(b) **After Option Exercise**. After Option exercise, Biogen Idec will be solely responsible for the costs and expenses related to the Development, Manufacture and Commercialization of Products.

1.5. **Supply Chain Strategy**.

1.5.1. **Clinical Supplies by Isis**. Prior to Option exercise, Isis will supply Clinical Supplies for the Clinical Studies under the ISIS-DMPK$_{Rx}$ R&D Plan. If Biogen Idec exercises the Option at least [***] prior to the planned Initiation of the PoC Trial, Biogen Idec may elect to either have (a) Isis supply Clinical Supplies for the PoC Trial, in which case Biogen Idec will pay Isis an amount equal to [***], or (b) a CMO supply Clinical Supplies for the PoC Trial in accordance with the Manufacturing Agreement entered into with such CMO. If Biogen Idec exercises the Option prior to, but less than [***] before, the planned Initiation of the PoC Trial, Isis will supply Clinical Supplies for the PoC Trial and Biogen Idec will pay Isis an amount equal to [***].

1.5.2. **Selecting a CMO**. Within [***] after Initiation of the PoC Trial or, if Biogen Idec exercises the Option prior to the Initiation of the PoC Trial, at such earlier time as the Parties may agree, the Parties will discuss in good faith a supply chain strategy to ensure adequate supply of Clinical Supplies for any Clinical Studies to be conducted after Option exercise and API and finished drug Product for Commercialization of a Product ("***Commercial Supplies***"), including selection of a CMO to supply or re-supply such Clinical Supplies or Commercial Supplies, validation batches and support for filings with applicable Regulatory Authorities in support of obtaining Approval, pursuant to the terms of a written agreement with a CMO. Notwithstanding the foregoing, Biogen Idec will have the right to select one or more CMOs to manufacture Clinical Supplies for any Clinical Studies to be conducted after Option exercise and Commercial Supplies and enter into Manufacturing Agreements with such CMO(s) in accordance with Section 1.5.3.

1.5.3. **Executing CMO Agreements**. In connection with Biogen Idec's selecting and engaging one or more CMOs under Section 1.5.2 above, the Parties will cooperate in good faith to negotiate and execute any agreements with CMOs for the Manufacture of Clinical Supplies as well as the toll Manufacture of Commercial Supplies (each such agreement, a "***Manufacturing Agreement***"). As between Biogen Idec and Isis, Biogen Idec will enter into such Manufacturing Agreements

with CMOs. The Manufacturing Agreements will include (1) a license from Isis to [***] under the [***] to the extent necessary for [***] (a "***Manufacturing License***"), which Isis agrees it shall grant to [***], or, at Biogen Idec's election, a sublicense from Biogen Idec to [***] and (2) [***]. Absent any such [***], except as set forth in this Section 1.5.3, Isis will have no obligations under such Manufacturing Agreements. Biogen Idec will have the final decision-making authority regarding [***]. Prior to execution of any such Manufacturing Agreement, Biogen Idec will provide a copy of any proposed Manufacturing Agreement to Isis for Isis' review and will consider in good faith all comments and recommendations provided by Isis with respect to such Manufacturing Agreement. Biogen Idec will provide Isis with a true and complete copy of any Manufacturing Agreement with a CMO within 30 days after the execution thereof. Biogen Idec will be responsible for paying [***].

1.5.4. **Additional Activities Requested by Biogen Idec**. If Biogen Idec desires that either Isis or a Third Party [***] or conduct other work to support Approval of a Product, including [***], prior to Option exercise ("***Other Pre-Option Activities***"), subject to Section 1.4.1 and Section 1.4.2, Biogen Idec will pay the costs of conducting such work, including, the cost of Isis' time incurred in performing such work at the then-applicable Isis FTE Rate, plus any reasonable out-of-pocket expenses incurred by Isis in performing such work ("***Other Pre-Option Costs***"). Isis will permit Biogen Idec to review, negotiate (with Isis) and approve the Other Pre-Option Costs prior to conducting any Other Pre-Option Activities. Isis will invoice Biogen Idec directly for any such approved Other Pre-Option Costs incurred by Isis and Biogen Idec will pay the invoices submitted pursuant to this Section 1.5.4 for such approved Other Pre-Option Costs within 45 days after receipt of the applicable invoice by Biogen Idec. In the case where Other Pre-Option Activities are performed by a Third Party, the Parties will arrange for the Third Party to directly bill Biogen Idec and for Biogen Idec to pay such Third Party directly.

1.6. **Biogen Idec's Participation in Regulatory Meetings**. During the Option Period, Isis will provide Biogen Idec with as much advance written notice as practicable of any meetings Isis has or plans to have with a Regulatory Authority regarding pre-approval or Approval matters for a Product and

will allow Biogen Idec to participate in any such meetings as an observer. In addition, Isis will provide Biogen Idec with minutes of any meeting Isis has with a Regulatory Authority that relates to a Product.

1.7. **Impact of [***] Development Path**. If the Parties mutually agree to amend the ISIS-DMPK$_{Rx}$ R&D Plan where such amended plan contemplates [***], then the Parties will make appropriate changes to the operational terms of this Agreement (e.g., [***]) to reflect such an [***] development plan, consistent with the comparable provisions necessary to support the development plan under the [***].

ARTICLE 2.
EXCLUSIVITY COVENANTS

2.1. **Exclusivity; Right of First Negotiation**.

2.1.1. **Exclusivity Covenants**.

(a) **The Parties' Exclusivity Covenants During the Option Period**. Each Party agrees that, except in the performance of its obligations under this Agreement and except as set forth in Section 2.1.2, Section 2.1.3, Section 10.4.2 or Section 10.4.3, it will not work independently or for or with any of its Affiliates or any Third Party (including the grant of any license to any Third Party) with respect to discovery, research, development, manufacture or commercialization of an ASO that is designed to bind to the RNA that encodes DMPK in the Field from the Effective Date through the expiration or earlier termination of the Option (the "***Option Period***").

(b) **Isis' Exclusivity Covenant After Option Exercise**. Except as set forth in Section 2.1.2, Section 2.1.3, Section 10.4.2 or Section 10.4.3, if Biogen Idec timely exercises the Option in accordance with this Agreement, then Isis will not work independently or for or with any of its Affiliates or any Third Party (including the grant of any license to any Third Party) with respect to:

(i) discovery, research or development of an ASO that is designed to bind to the RNA that encodes DMPK in the Field until [***]; and

(ii) on a country-by-country basis, commercializing an ASO that is designed to bind to the RNA that encodes DMPK in the Field until [***].

(c) **Biogen Idec's Exclusivity Covenant After Option Exercise**. After Option exercise, Biogen Idec's exclusivity obligations under Section 2.1.1(a) will be extended and will continue for so long as and to the extent of [***].

Except as expressly set forth in Section 2.1.2, Section 2.1.3, or Section 10.4.3, in no event will Isis have the right to [***].

2.1.2. **Right of First Negotiation for Follow-On Compounds**. During the period commencing on the Effective Date and ending upon (i) if the Option is not exercised in accordance with this Agreement, [***], or (ii) if the Option is exercised in accordance with this Agreement, [***] (such period, the "***ROFN Period***"), Isis hereby grants to Biogen Idec a right of first negotiation to develop and commercialize any Follow-On Compound developed by or on behalf of Isis, which right of first negotiation is granted on the following terms and conditions:

(a) Within [***], Biogen Idec may provide Isis with a non-binding, good faith written notice expressing Biogen Idec's desire for Isis to identify a Follow-On Compound (a "***Follow-On Interest Notice***"). If (i) Biogen Idec does not, within such [***] period, provide Isis with a Follow-On Interest Notice, or (ii) Biogen Idec does timely provide Isis with a Follow-On Interest Notice but the Parties do not agree on a [***] related to such Follow-On Compound by 5:00 pm (Eastern Time) on the [***] following the date of Option exercise, then, Isis may work independently or with any of its Affiliates or any Third Party with respect to the discovery, research, development and manufacture of a Follow-On Compound; *provided*, *however*, that during the ROFN Period, Isis will not grant any license (or an option to obtain such a license) under any intellectual property owned, controlled or licensed by Isis to make, use or sell any Follow-On Compound (a "***Follow-On Agreement***") *unless and until* Isis provides a written notice to Biogen Idec (a "***Follow-On Negotiation Notice***"), which notice identifies [***]. Isis will not initiate negotiations regarding or enter into such a Follow-On Agreement with any Third Party until [***] (each, a "***ROFN Termination Event***").

(b) If Biogen Idec or one of its Affiliates responds within [***] after its receipt of the Follow-On Negotiation Notice indicating that Biogen Idec or one of its Affiliates desires to negotiate with Isis regarding the proposed Follow-On Agreement, Isis and Biogen Idec or one of its Affiliates will negotiate in good faith with each other until the [***] after the date Isis provided Biogen Idec the Follow-On Negotiation Notice (or such other period as mutually agreed by the Parties) (the "***Negotiation Period***") regarding a mutually satisfactory Follow-On Agreement (which may take the form of an amendment to this Agreement). During the Negotiation Period, Isis will make at least [***] to Biogen Idec or its Affiliate setting forth all material business and legal terms on which Isis would be willing to enter into the proposed Follow-On Agreement with Isis; *provided, that* neither Party will have any obligation to enter into a Follow-On Agreement. If the Negotiation Period expires before Biogen Idec or its Affiliate and Isis have entered into such a Follow-On Agreement, Isis will have no further obligation to negotiate with Biogen Idec or its Affiliates with respect to such Follow-On Agreement and Isis will be free to negotiate and enter an agreement with a Third Party with respect to a Follow-On Agreement [***]; *provided*, *however*, that Isis will not enter into any such Follow-On Agreement with any Third Party unless the terms and pricing of such Follow-On Agreement, [***] during the Negotiation Period. If, with respect to any Follow-On Compound that was the subject of the Follow-On Agreement previously discussed by the Parties, after the end of the Negotiation Period and prior to Isis entering into a Follow-On Agreement with a Third Party, [***] regarding the

Follow-On Compound, Isis' obligations and Biogen Idec's rights under Section 2.1.2(a) and this Section 2.1.2(b) will reset and Isis will provide Biogen Idec with a new Follow-On Negotiation Notice.

(c) Any Follow-On Agreement entered into by Isis with a Third Party in accordance with Section 2.1.2(b) will be a Permitted License to the extent related to the Follow-On Compound.

(d) Notwithstanding anything to the contrary in this Agreement, until [***], Isis will provide to Biogen Idec a Follow-On Negotiation Notice for each [***] pursuant to this Section 2.1.2, *unless* Isis enters into a Follow-On Agreement with a Third Party pursuant to this Section 2.1.2 and the terms of such agreement do not permit Isis to grant Biogen Idec rights with respect to the applicable Follow-On Compound.

2.1.3. **Limitations and Exceptions to Isis' Exclusivity Covenants**. Notwithstanding anything to the contrary in this Agreement, Isis' practice of the following will not violate Section 2.1.1 or Section 2.1.2:

(a) Any activities pursuant to the Prior Agreements as in effect on the Effective Date; and

(b) The granting of, or performance of obligations under, Permitted Licenses.

2.2. **Effect of Exclusivity on Indications**. The Compounds are designed to bind to the RNA that encodes DMPK in the Field, which is known to play a role in Myotonic Dystrophy-Type 1. Isis and Biogen Idec are subject to exclusivity obligations under Section 2.1; *however*, the Parties acknowledge and agree that each Party (on its own or with a Third Party) may continue to discover, research, develop, manufacture and commercialize products that are designed to bind to the RNA that encodes a gene that is *not* DMPK for any indication, even if such products are designed to treat Myotonic Dystrophy-Type 1.

ARTICLE 3.
EXCLUSIVE OPTION

3.1. **Option**.

3.1.1. **Advance Data Disclosure**. On or about 90 days before the date estimated by Isis that the database will be locked for the PoC Trial ("***Estimated Lock Date***"), Isis will provide Biogen Idec with a written notice of such Estimated Lock Date. If Biogen Idec provides written notice to Isis [***] after Biogen Idec's receipt of the notice regarding the Estimated Lock Date that Biogen Idec has a good faith intention to exercise the Option under Section 3.1.3, then as soon as reasonably practicable after Isis receives such notice from Biogen Idec, Isis will provide Biogen Idec with an early preview of the information to be included in the [***] to the extent then in Isis' possession and not already provided to Biogen Idec, to

assist Biogen Idec with its decision of whether to exercise the Option. Within 15 Business Days after Biogen Idec's receipt of such data, Biogen Idec will provide Isis with a [***] notice of whether Biogen Idec still intends to exercise the Option, *provided, however*, that Biogen Idec's failure to do so will not be deemed a breach of this Agreement.

3.1.2. **PoC Trial Completion Notice**. Isis will provide to Biogen Idec or its designated Affiliate (i) a copy of the most recent Investigator's Brochure for the Product, (ii) written notice from Isis regarding completion of the PoC Trial, and (iii) the PoC Data Package, to the extent not already provided to Biogen Idec under Section 3.1.1 above (such notice and package, a "***PoC Trial Completion Notice***") promptly, and in any event within 30 days after database lock for the PoC Trial. Within 15 days of receipt of the PoC Trial Completion Notice, Biogen Idec or an Affiliate will notify Isis of any omissions or deficiencies that Biogen Idec or its Affiliate believes in good faith cause the PoC Trial Notice to be incomplete ("***Deficiency Notice***"). Isis will promptly, and in any event within 15 days of receipt of the Deficiency Notice, resubmit a complete PoC Trial Completion Notice to Biogen Idec or its designated Affiliate, including any information required to be included in the PoC Data Package that Biogen Idec identified in the Deficiency Notice. If the Parties do not agree as to whether the PoC Trial Completion Notice is complete, the matter will be referred to the Executives for resolution. The Executives will meet promptly and negotiate in good faith to resolve the dispute and agree upon a complete PoC Trial Completion Notice.

3.1.3. **Option and Option Deadline**. Isis hereby grants to Biogen Idec and its Affiliates an exclusive option to obtain the license set forth in Section 4.1.1 (the "***Option***"). The Option will be available to Biogen Idec and its Affiliates until 5:00 pm (Eastern Time) on the [***] following Biogen Idec's receipt of a complete PoC Trial Completion Notice (the "***Option Deadline***"); *provided, however*, if Biogen Idec determines that an HSR Filing is required to be made under the HSR Act to exercise the Option and notifies Isis of such determination within [***] after Biogen Idec's receipt of the complete PoC Trial Completion Notice, the Parties will promptly file an HSR Filing in accordance with Section 3.1.4 and the Option Deadline will be extended until 5:00 pm (Eastern Time) on the fifth Business Day after the HSR Clearance Date. If, by the Option Deadline, Biogen Idec or its designated Affiliate (i) notifies Isis in writing that it wishes to exercise the Option, and (ii) pays to Isis the license fee set forth in Section 6.3, Isis will, and hereby does, grant to Biogen Idec or its designated Affiliate the license set forth in Section 4.1.1. If, by the Option Deadline, Biogen Idec or its designated Affiliate has not both (y) provided Isis a written notice stating that Biogen Idec is exercising its Option, and (z) paid Isis the license fee in accordance with Section 6.3, then Biogen Idec's Option will expire.

3.1.4. HSR Compliance.

(a) **HSR Filing**. If Biogen Idec notifies Isis pursuant to Section 3.1.3 that an HSR Filing is required to exercise the Option under this Agreement, each of Biogen Idec and Isis will, within five Business Days after such notice from Biogen Idec (or such later time as may be agreed to in writing by the Parties), file with the United States Federal Trade Commission ("***FTC***") and the Antitrust Division of the United States Department of Justice ("***DOJ***"), any HSR Filing required with respect to the transactions contemplated hereby. The Parties will cooperate with one another to the extent necessary in the preparation of any such HSR Filing. Each Party will be responsible for its own costs and expenses (other than filing fees, which Biogen Idec will pay) associated with any HSR Filing.

(b) **HSR Clearance**. In furtherance of obtaining HSR Clearance for an HSR Filing filed under Section 3.1.4(a), Isis and Biogen Idec will use their respective commercially reasonable efforts to resolve as promptly as practicable any objections that may be asserted with respect to this Agreement or the transactions contemplated by this Agreement under any antitrust, competition or trade regulatory law. In connection with obtaining such HSR Clearance from the FTC, the DOJ or any other governmental authority, Biogen Idec and its Affiliates will not be required to (i) sell, divest (including through a license or a reversion of licensed or assigned rights), hold separate, transfer or dispose of any assets, operations, rights, product lines, businesses or interest therein of Biogen Idec or any of its Affiliates (or consent to any of the foregoing actions); or (ii) litigate or otherwise formally oppose any determination (whether judicial or administrative in nature) by a governmental authority seeking to impose any of the restrictions referenced in clause (i) above.

3.2 Restrictions on Isis' Right to Grant Diagnostic Rights; Right to Negotiate Diagnostic Rights.

3.2.1 Isis hereby grants to Biogen Idec and its Affiliates an option (the "***Diagnostic Option***") to negotiate during the Full Royalty Period the terms of an agreement under which [***]. The Diagnostic Option will be available to Biogen Idec and its Affiliates until the expiration of the [***].

3.2.2 During the [***], Isis (i) has the right to [***], and (ii) will not [***].

3.2.3 If, during the [***], Isis grants any Third Party a [***], then Isis will promptly notify Biogen Idec of such [***] and will offer Biogen Idec a [***].

ARTICLE 4.
LICENSE GRANTS TO BIOGEN IDEC

4.1. License Grants to Biogen Idec.

4.1.1. Development and Commercialization License. Subject to the terms and conditions of this Agreement, effective upon Biogen Idec's exercise of the Option in accordance with this Agreement, Isis grants to Biogen Idec a worldwide, exclusive, royalty-bearing, sublicensable (in accordance with Section 4.1.2 below) license under the Licensed Technology to research, Develop, Manufacture, have Manufactured (in accordance with Section 4.1.2 below), register, market and Commercialize Products in the Field.

4.1.2. Sublicense Rights.

(a) Subject to the terms and conditions of this Agreement, Biogen Idec will have the right to grant sublicenses under the license granted under Section 4.1.1 above:

(i) under the Isis Core Technology Patents, Isis Product-Specific Patents and Isis Know-How to an Affiliate of Biogen Idec or a Third Party; and

(ii) under the Isis Manufacturing and Analytical Patents and Isis Manufacturing and Analytical Know-How solely to (y) [***] or (z) [***];

provided that each such sublicense will be subject to, and consistent with, the terms and conditions of this Agreement. If, within 90 days of first learning of any breach of such sublicense terms, Biogen Idec fails to take any action to enforce the sublicense terms of a sublicense granted pursuant to this Section 4.1.2, which failure would cause an adverse effect on Isis, Biogen Idec hereby grants Isis the right to enforce such sublicense terms on Biogen Idec's behalf and will cooperate with Isis (which cooperation will be at Biogen Idec's sole expense and will include, Biogen Idec joining any action before a court or administrative body filed by Isis against such Sublicensee if and to the extent necessary for Isis to have legal standing before such court or administrative body) in connection with enforcing such terms. Biogen Idec will provide Isis with a true and complete copy of any sublicense granted pursuant to this Section 4.1.2 within 30 days after the execution thereof. Notwithstanding the foregoing, if Isis fails to comply with the terms of Section 1.5.3 and does not cure such failure within 90 days after written notice from Biogen Idec specifying the details of any such failure, Biogen Idec will have the right to grant a sublicense under the Isis Manufacturing and Analytical Patents and Isis Manufacturing and Analytical Know-How to [***].

(b) **Effect of Termination on Sublicenses**. If this Agreement terminates for any reason, any Sublicensee will, from the effective date of such termination, automatically become a direct licensee of Isis with respect to the rights sublicensed to the Sublicensee by Biogen Idec; *so long as* (i) such Sublicensee is not in breach of its sublicense agreement, (ii) such

Sublicensee agrees in writing to comply with all of the terms of this Agreement to the extent applicable to the rights originally sublicensed to it by Biogen Idec, and (iii) such Sublicensee agrees to pay directly to Isis such Sublicensee's payments under this Agreement to the extent applicable to the rights sublicensed to it by Biogen Idec. Biogen Idec agrees that it will confirm clause (i) of the foregoing in writing at the request and for the benefit of Isis and if requested, the Sublicensee.

4.1.3. **No Implied Licenses**. All rights in and to Licensed Technology not expressly licensed to Biogen Idec under this Agreement are hereby retained by Isis or its Affiliates. All rights in and to Biogen Idec Technology not expressly licensed or assigned to Isis under this Agreement, are hereby retained by Biogen Idec or its Affiliates. Except as expressly provided in this Agreement, no Party will be deemed by estoppel or implication to have granted the other Party any license or other right with respect to any intellectual property.

4.1.4. **License Conditions; Limitations**. Subject to Section 6.8, any license granted under Section 4.1.1 and the sublicense rights under Section 4.1.2 are subject to and limited by (i) any applicable Third Party Obligations, (ii) the Prior Agreements, and (iii) the Isis In-License Agreements, in each case to the extent the provisions of such obligations or agreements are specifically disclosed to Biogen Idec in writing (or via electronic data room) prior to Biogen Idec's exercise of the Option. Isis will disclose to Biogen Idec any Third Party Obligations Isis believes apply to the Product each time Isis provides Biogen Idec with (x) the [***]; (y) the [***]; and (z) [***], and Biogen Idec will have the right to elect to exclude any Third Party Patent Rights and Know-How to which such Third Party Obligations apply by providing Isis written notice prior to Option exercise. If, prior to Option exercise, Biogen Idec provides Isis with such a written notice to exclude certain Third Party Patent Rights and Know-How, such Third Party Patent Rights and Know-How will not be included in the Licensed Technology licensed under this Agreement. If Biogen Idec does not provide Isis with such a written notice to exclude such Third Party Patent Rights and Know-How prior to Option exercise, such Third Party Patent Rights and Know-How (and any Third Party Obligations to the extent applicable to Products) will be included in the Licensed Technology licensed under this Agreement.

4.1.5. **Trademarks for Products**. If Biogen Idec exercises its Option hereunder, to the extent that (i) Isis owns any trademark(s) specific to a Product which Isis used prior to the exercise of the Option, and (ii) Biogen Idec reasonably believes such trademark(s) would be necessary or useful for the marketing and sale of a Product, then upon Biogen Idec's request and at Biogen Idec's sole cost and expense relating to such assignment, Isis will assign its rights and title to such trademark(s) to Biogen Idec or one or more designated Affiliates sufficiently in advance of the First Commercial Sale of a Product to enable Biogen Idec or its Affiliates to offer such Product for sale under such trademark(s). Other than trademarks owned by Isis prior to the exercise of the Option, Biogen Idec or its

designated Affiliate will be solely responsible for developing, selecting, searching, registering and maintaining, and, subject to Section 10.4, will be the exclusive owner of, all trademarks, trade dress, logos, slogans, designs, copyrights and domain names used on or in connection with Products.

4.2. **Assignment of Isis Product-Specific Patents; Grant Back to Isis**.

4.2.1. After Biogen Idec has obtained the license under Section 4.1.1 and following review and consideration by the Joint Patent Committee, Isis will assign to Biogen Idec or one or more of its designated Affiliates, Isis' ownership interest in (i) all Isis Product-Specific Patents that are owned by Isis (whether solely owned or jointly owned with one or more Third Parties), and (ii) any Jointly-Owned Program Patents Covering Products, and thereafter, subject to Section 7.2.4, Isis will have no further right to control any aspect of the Prosecution and Maintenance of such Isis Product Specific Patents and such Jointly-Owned Program Patents. The assignment of Patent Rights assigned in this Section 4.2.1 will occur within 30 days of Biogen Idec obtaining the license under Section 4.1.1.

4.2.2. Biogen Idec grants to Isis a worldwide, exclusive, sublicensable license under any Isis Product Specific Patents and Jointly-Owned Program Patents assigned to Biogen Idec under Section 4.2.1, (i) for all [***], and (ii) to [***] to the extent permitted by this Agreement.

4.3. **Ownership of and Assistance with Regulatory Filings**. [***] prior to the date on which Biogen Idec reasonably anticipates filing an NDA or MAA covering the Product, Isis' and Biogen Idec's regulatory teams will meet and begin to prepare a plan, which plan will be complete no later than [***] prior to such anticipated filing date, for drafting and reviewing the sections of the NDA and MAA for the Product (including establishing responsibilities for drafting and reviewing common technical document ("***CTD***") modules, authorship, plan activity timelines and associated costs and expenses) to ensure a smooth transition to Biogen Idec, accelerate CTD completion and facilitate rapid NDA and MAA filing. The Parties will act in good faith and mutually agree upon such a plan, *provided, however*, that, after Option exercise, Biogen Idec will have final decision making authority with respect to the [***]. Once such plan is complete, each Party will use Commercially Reasonable Efforts to execute their respective tasks and responsibilities under such plan in the time frames set forth in such plan. After Option exercise, if Biogen Idec requests, Isis will assist Biogen Idec in preparing regulatory filings for the Product, under terms negotiated in good faith between Isis and Biogen Idec, including payment for Isis' time at Isis' then applicable FTE Rate plus any reasonable out of pocket expenses incurred by Isis in providing such assistance.

4.4. **Subcontracting**. Subject to the terms of this Section 4.4, each Party will have the right to engage Third-Party subcontractors to perform certain of its obligations under this Agreement. Any subcontractor to be engaged by a Party to perform a Party's obligations set forth in the Agreement will meet the qualifications typically required by such Party for the performance of work similar in scope and complexity to the subcontracted activity

and will enter into such Party's standard nondisclosure agreement consistent with such Party's standard practices. Any Party engaging a subcontractor hereunder will remain responsible and obligated for such activities and will not grant rights to such subcontractor that interfere with the rights of the other Party under this Agreement.

4.5. **Technology Transfer after Option Exercise**. Isis will promptly, but no later than [***] after Biogen Idec exercises its Option hereunder, deliver to Biogen Idec or one or more designated Affiliates:

4.5.1. **Isis Know-How**. All Isis Know-How in Isis' possession that has not previously been provided hereunder, for use solely in accordance with the licenses granted under Section 4.1.1 and Section 10.4.1(b), including transferring the IND for the Development Candidate to Biogen Idec together with all regulatory documentation (including drafts) related to the Development Candidate. To assist with the transfer of such Isis Know-How, Isis will make its personnel reasonably available to Biogen Idec during normal business hours for up to [***] ([***]) of Isis' time to transfer such Isis Know-How under this Section 4.5.1. Thereafter, if requested by Biogen Idec, Isis will provide Biogen Idec with a reasonable level of assistance in connection with such transfer, which Biogen Idec will reimburse Isis for its time incurred in providing such assistance at the then-applicable Isis FTE Rate, plus any reasonable out-of-pocket expenses incurred by Isis in providing such assistance.

4.5.2. **Isis Manufacturing and Analytical Know-How**. Solely for use by Biogen Idec, its Affiliates or a Third Party acting on Biogen Idec's behalf to Manufacture API in Biogen Idec's own or an Affiliate's manufacturing facility, all Isis Manufacturing and Analytical Know-How in Isis' Control relating to Products, which is necessary for the exercise by Biogen Idec, its Affiliates or a Third Party of the Manufacturing rights granted under Section 4.1.1. Upon Biogen Idec's request, subject to Section 4.1.2, Isis will provide up to [***] for [***] ([***]) of its time to transfer such Manufacturing and Analytical Know-How under this Section 4.5.2 to any Third Party Manufacturing API or finished Product on Biogen Idec's behalf solely to Manufacture API or finished Product in accordance with the terms of this Agreement. Thereafter, if requested by Biogen Idec, Isis will provide Biogen Idec with a reasonable level of assistance in connection with such transfer, which Biogen Idec will reimburse Isis for its time incurred in providing such assistance at the then-applicable Isis FTE Rate, plus any reasonable out-of-pocket expenses incurred by Isis in providing such assistance.

4.5.3. **API and Product**. Upon Biogen Idec's written request, Isis will sell to Biogen Idec any bulk API and finished drug Product in Isis' possession at the time of Option exercise, at a price equal to [***].

ARTICLE 5.
DEVELOPMENT, MANUFACTURING AND COMMERCIALIZATION

5.1. **Biogen Idec Diligence**. Following Option exercise, Biogen Idec will be solely responsible for all Development, Manufacturing and Commercialization activities, and for all costs and expenses associated therewith, with respect to the Development, Manufacture and Commercialization of Products; and Biogen Idec will use Commercially Reasonable Efforts to Develop, Manufacture and Commercialize Products.

5.1.1. **Specific Performance Milestone Events**. Without limiting any of the foregoing, following Option exercise, Biogen Idec will use Commercially Reasonable Efforts to achieve the specific performance milestone events set forth in SCHEDULE 5.1.1 ("***Specific Performance Milestone Events***") for a Product on the timeline set forth in SCHEDULE 5.1.1; *provided*, *however*, [***].

5.1.2. **Integrated Development Plan**. Biogen Idec will prepare a Development and global integrated Product plan outlining key aspects of the Development of each Product through Approval as well as key aspects of worldwide regulatory strategy, market launch, and Commercialization ("***Integrated Development Plan***" or "***IDP***"). Biogen Idec will prepare the IDP no later than [***] after Option exercise, and the IDP will contain information consistent with Biogen Idec's Development and Commercialization plans for its similar products at similar stages of development. Once Biogen Idec has prepared such plans, Biogen Idec will update the IDP consistent with Biogen Idec's standard practice and provide such updates to Isis [***]. Biogen Idec and Isis will meet [***] basis to discuss the draft of the IDP and Biogen Idec will consider, in good faith, any proposals and comments made by Isis for incorporation in the final IDP. Notwithstanding the foregoing, Biogen Idec's obligations to provide Isis with information or reports under this Section 5.1.2 will terminate if [***].

5.1.3. **Investigator's Brochure**. Upon Option exercise, Isis will provide to Biogen Idec an up-to-date version of the Investigator's Brochure. After Option Exercise, Biogen Idec will keep Isis reasonably informed with respect to the status, activities and progress of Development of Products by providing updated versions of the Investigator's Brochure to Isis [***] and when Development of the Products results in any substantive change to the safety or risk to the Products. Biogen Idec's obligations under this Section 5.1.3 will terminate if [***].

5.1.4. **Isis' Participation in Regulatory Meetings**. Biogen Idec will provide Isis with as much advance written notice as practicable of any meetings Biogen Idec has or plans to have with a Regulatory Authority regarding pre-approval or Approval matters for a Product or that directly relate to Isis' antisense oligonucleotide chemistry platform, and will allow Isis to participate in any such meetings as an observer.

5.1.5. **Regulatory Communications**. Biogen Idec will provide Isis with copies of documents and communications submitted to (including drafts thereof) and received from Regulatory Authorities [***] that materially impact the Development or Commercialization of Products for Isis' review and comment, and Biogen Idec will consider in good faith including any comments provided by Isis to such documents and communications.

5.1.6. **Class Generic Claims**. To the extent Biogen Idec intends to make any claims in a Product label or regulatory filing that are class generic to ASOs, Biogen Idec will provide such claims and regulatory filings to Isis in advance and will consider in good faith any proposals and comments made by Isis, *provided*, *however*, that Biogen Idec is not obligated to incorporate such proposals and comments in any such claims and regulatory filings.

5.1.7. **Applicable Laws**. Biogen Idec will perform its activities pursuant to this Agreement in compliance with good laboratory and clinical practices and cGMP, in each case as applicable under the laws and regulations of the country and the state and local government wherein such activities are conducted.

5.2. **Global Safety Database; Pharmacovigilance Agreement**.

5.2.1. **Pharmacovigilance Agreement**. As soon as reasonably practicable following designation of the Development Candidate, and in any event no later than [***] prior to the date on which Isis anticipates filing an IND for the Product with a Regulatory Authority, the Parties will enter into a Safety Drug Exchange Agreement relating to the collection, review, assessment, tracking, exchange and filing of information related to adverse events associated with a Product occurring prior to the First Commercial Sale in any country on terms substantially the same as the terms of the Safety Drug Exchange Agreement to be entered into by the Parties with respect to adverse events associated with products developed under the SMN Agreement. No later than 30 days prior the date on which Biogen reasonably anticipates that it will exercise the Option, Biogen Idec shall so notify Isis and the pharmacovigilance departments of each of Isis and Biogen Idec will meet and determine the approach to be taken for the collection, review, assessment, tracking, exchange and filing of information related to adverse events associated with a Product occurring after such First Commercial Sale, consistent with the provisions of this Section 5.2. Such approach will be documented in a separate and appropriate written pharmacovigilance agreement between the Parties which will control with respect to the subject matter covered therein (the "***Pharmacovigilance Agreement***"). Such agreement will specify that the owner of the IND for a Product will be the global commercial safety database owner for such Product with primary responsibility for maintaining such database, and that Isis will be and remain the owner of the Isis Internal ASO Safety Database with primary responsibility for maintaining such database. Such agreement will also specify that, prior to Biogen Idec's exercise of the Option, Biogen Idec may suggest actions to address audit findings, and Isis will consider all such suggestions in good faith. The Pharmacovigilance Agreement will be in accordance with, and will enable the Parties and their Affiliates or licensees or Sublicensees, as applicable, to fulfill, local and international regulatory reporting obligations to Regulatory Authorities and other Applicable Law.

5.2.2. **Isis' Antisense Safety Database**.

(a) Isis maintains an internal database that includes information regarding the tolerability of its drug compounds, individually and as a class, including information discovered during pre-clinical and clinical development (the "***Isis Internal ASO Safety Database***"). In an effort to maximize understanding of the safety profile and pharmacokinetics of Isis compounds, after Biogen Idec exercises its Option, Biogen Idec will cooperate in connection with populating the Isis Internal ASO Safety Database. To the extent collected by Biogen Idec and in the form in which Biogen Idec uses/stores such information for its own purposes, Biogen Idec will provide Isis with information concerning toxicology, pharmacokinetics, safety pharmacology study(ies), serious adverse events and other safety information related to Products as soon as practicable following the date such information is available to Biogen Idec (but not later than 30 days after Biogen Idec's receipt of such information). In connection with any reported serious adverse event, Biogen Idec will provide Isis all serious adverse event reports, including initial, interim, follow-up, amended, and final reports. In addition, with respect to Products, Biogen Idec will provide Isis with copies of Annual safety updates filed with each IND and the safety sections of any final Clinical Study reports within 30 days following the date such information is filed or is available to Biogen Idec, as applicable. Furthermore, Biogen Idec will promptly provide Isis with any supporting data and answer any follow-up questions reasonably requested by Isis. All such information disclosed by Biogen Idec to Isis will be Biogen Idec Confidential Information; *provided*, *however*, that Isis may disclose any such Biogen Idec Confidential Information to (i) Isis' other partners pursuant to Section 5.2.2(b) below if such information is regarding class generic properties of ASOs, or (ii) any Third Party, in each case, so long as Isis does not disclose the identity of a Product or Biogen Idec. Biogen Idec will deliver all such information to Isis for the Isis Internal ASO Safety Database to Isis Pharmaceuticals, Inc., 2855 Gazelle Court, Carlsbad, California 92010, Attention: Chief Medical Officer (or to such other address/contact designated in writing by Isis). Biogen Idec will also cause its Affiliates and Sublicensees to comply with this Section 5.2.2(a).

(b) From time to time, Isis utilizes the information in the Isis Internal ASO Safety Database to conduct analyses to keep Isis and its partners informed regarding class generic properties of ASOs, including with respect to safety. As such, if and when Isis identifies safety or other related issues that may be relevant to a Product (including any potential class-related toxicity), Isis will promptly inform Biogen Idec of such issues and, if requested, provide the data supporting Isis' conclusions.

ARTICLE 6.
FINANCIAL PROVISIONS

6.1. **Option Fee**. In partial consideration for Biogen Idec's Option hereunder, within five Business Days following the Effective Date, Biogen Idec will pay Isis an Option fee equal to $12,000,000.

6.2. **Milestone Payments for Achievement of Pre-Licensing Milestone Events**. As further consideration for Biogen Idec's Option, Biogen Idec will pay to Isis the milestone payments as set forth in TABLE 1 below when a milestone event (each, a "***Pre-Licensing Milestone Event***") listed in TABLE 1 is first achieved by a Product:

TABLE 1

Pre-Licensing Milestone Event	Milestone Event Payment
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]

Biogen Idec will pay to Isis the Milestone Event payments as set forth in TABLE 1 after the applicable Milestone Event is first achieved by a Product, even if Biogen Idec has exercised the Option prior to achievement of the Milestone Event; *provided*, *however*, that if Biogen Idec exercises the Option prior to achievement of the [***] Milestone Event, then the milestone payment for achievement of the [***] Milestone Event will be [***].

6.3. **License Fee**. Together with Biogen Idec's written notice to Isis stating that Biogen Idec is exercising its Option in accordance with this Agreement, Biogen Idec will pay to Isis a license fee of $[***]; *provided, however*, that if Biogen Idec exercises the Option prior to the [***], the license fee will be [***].

6.4 **Milestone Payments for Achievement of Post-Licensing Milestone Events**. Biogen Idec will pay to Isis the milestone payments as set forth in TABLE 2 below when a milestone event (each, a "***Post-Licensing Milestone Event***") listed in TABLE 2 is first achieved by a Product:

TABLE 2

Post-Licensing Milestone Event	Milestone Event Payment
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]

If Biogen Idec exercises the Option prior to the [***], Biogen Idec will pay to Isis [***] upon the earlier of (a) [***] or (b) [***]. For the avoidance of doubt, if such $[***] payment is paid pursuant to clause (b) of the preceding sentence, such payment will be in addition to the amount due upon the occurrence of the corresponding Post-Licensing Milestone Event under TABLE 2 above.

6.5. **Limitations on Milestone Payments; Exceptions; Notice**.

6.5.1. The $[***] milestone payment is [***] the first Milestone Event Payment for [***]. For example, if the [***] Milestone Event is achieved in the [***], then the milestone payment for such Milestone Event is [***] the first to occur of the (i) [***] (ii) [***] or (iii) [***] milestone payments.

6.5.2. Each milestone payment set forth in TABLE 1 and TABLE 2 above will be paid only once upon the first achievement of the Milestone Event regardless of how many Products achieve such Milestone Event.

6.5.3. If a particular Milestone Event is not achieved because Development activities transpired such that achievement of such earlier Milestone Event was unnecessary or did not otherwise occur, then upon achievement of a later Milestone Event the Milestone Event payment applicable to such earlier Milestone Event will also be due. For example, if a Party proceeds directly to [***] without achieving the [***] then upon achieving the [***] Milestone Event, both the [***] and [***] Milestone Event payments are due.

6.5.4. Each time a Milestone Event is achieved under this ARTICLE 6, Biogen Idec will send Isis, or Isis will send Biogen Idec, as the case may be, a written notice thereof promptly (but no later than [***]) following the date of achievement of such Milestone Event and such payment will be due within [***] of the date such notice was delivered.

6.6. **Royalty Payments to Isis**.

6.6.1. **Biogen Idec Full Royalty**. As partial consideration for the rights granted to Biogen Idec hereunder, subject to the provisions of this Section 6.6.1 and Section 6.6.2, Biogen Idec will pay to Isis royalties on Annual worldwide Net Sales of Products sold by Biogen Idec, its Affiliates or Sublicensees, on a country-by-country basis, in each case in the amounts as follows in TABLE 3 below (the "***Biogen Idec Full Royalty***"):

TABLE 3

Royalty Tier	Annual Worldwide Net Sales of Products	Royalty Rate
1	For the portion of Annual Worldwide Net Sales < $[***]	[***]%
2	For the portion of Annual Worldwide Net Sales ≥ $[***] but < $[***]	[***]%
3	For the portion of Annual Worldwide Net Sales ≥ $[***] but < $[***]	[***]%
4	For the portion of Annual Worldwide Net Sales ≥ $[***]	[***]%

Annual worldwide Net Sales will be calculated by [***].

(a) Biogen Idec will pay Isis royalties on Net Sales of Products arising from named patient and other similar programs under Applicable Laws, and Biogen Idec will provide reports and payments to Isis consistent with Section 6.9. No royalties are due on Net Sales of Products arising from compassionate use and other programs providing for the delivery of Product at no cost. The sales of Products arising from named patient, compassionate use, or other similar programs will not be considered a First Commercial Sale for purposes of calculating the Full Royalty Period.

(b) For purposes of clarification, any Isis Product-Specific Patents assigned to Biogen Idec as set forth in Section 4.2.1 will still be considered Isis Product-Specific Patents for determining the royalty term and applicable royalty rates under this ARTICLE 6.

6.6.2. **Application of Royalty Rates**. All royalties set forth under Section 6.6.1 are subject to the provisions of this Section 6.6.2, and are payable as follows:

(a) **Full Royalty Period**. Biogen Idec's obligation to pay Isis the Biogen Idec Full Royalty above with respect to a Product will continue on a country-by-country and Product-by-Product basis from the date of First Commercial Sale of such Product until the later of the date of expiration of (i) the last Valid Claim within the Licensed Patents Covering such Product in the country in which such Product is made, used or sold, (ii) the data exclusivity period conferred by the applicable Regulatory Authority in such country with respect to such Product (e.g., such as in the case of an orphan drug), or (iii) the [***] anniversary of the First Commercial Sale of such Product in such country (such royalty period, the "***Full Royalty Period***").

(b) **Competition from Generic Products**. Subject to Section 6.6.2(d), on a country-by-country and Product-by-Product basis, if, within the [***], a Generic Product is sold in a country, then the Biogen Idec Full Royalty rate used to pay Isis royalties on a Product in such country will be reduced to [***]% of the otherwise applicable Biogen Idec Full Royalty rate. For the purpose of determining the [***] under this Section 6.6.2(b), if requested by Biogen Idec, Isis and Biogen Idec will meet and confer and mutually agree upon the Parties' best estimate of when the Full Royalty Period [***] in each country where Products are being sold.

(c) **Reduced Royalty Period**. Subject to Section 6.6.2(d), on a country-by-country and Product-by-Product basis, after the expiration of the Full Royalty Period and until the end of the Reduced Royalty Period, in lieu of the royalty rates set forth in TABLE 3 of Section 6.6.1, Biogen Idec will pay Isis royalty rates (the "***Biogen Idec Reduced Royalty***") on Net Sales of Products calculated on a Calendar Year-by-Calendar Year basis by [***]; *provided, however*, that the Biogen Idec Reduced Royalty rate in each country will in no event exceed the [***].

(d) **Limitation on Aggregate Reduction for Biogen Idec Royalties**.

(i) In no event will the aggregate royalty reductions under Section 6.6.2(b) and Section 6.6.2(c) reduce the royalties payable to Isis on Net Sales of a Product in any given period to an amount that is less than [***].

(ii) In no event will the aggregate royalty offsets under Section 6.8.3(b) and Section 6.8.3(c) reduce the royalties payable to Isis on Net Sales of a Product in any given period to an amount that is less than the greater of [***].

For example, if the Royalty Quotient during a given Calendar Year in the Reduced Royalty Period is less than [***]%, then the offsets under Section 6.8.3(b) and Section 6.8.3(c) will not apply during such Calendar Year but the full Royalty Quotient reduction pursuant to Section 6.6.2(c) will apply.

As an additional example, if the Royalty Quotient during a given Calendar Year in the Reduced Royalty Period is [***]%, and the [***] in such Calendar Year are [***]% of the applicable royalty rates in TABLE 3 of Section 6.6.1, then Biogen Idec may apply the offsets under Section 6.8.3(b) and Section 6.8.3(c) until the actual royalty payment made to Isis in such Calendar Year is equal to [***]% of the applicable royalty rates in TABLE 3 of Section 6.6.1.

(e) **End of Royalty Obligation**. On a country-by-country basis, other than [***], Biogen Idec's obligation to make royalty payments hereunder in such country will end on the expiration of the Reduced Royalty Period in such country. "***Reduced Royalty Period***" means, on a country by country basis, the period commencing upon the expiration of the [***] in such country and ending when the [***].

(f) **Royalty Examples**. SCHEDULE 6.6.2(f) attached hereto contains examples of how royalties will be calculated under this Section 6.6.

(g) **Allocation of Net Sales**. If, by reason of one or more royalty rate adjustments under this Section 6.6.2, different royalty rates apply to Net Sales of Products from different countries, Biogen Idec will [***] such Net Sales [***]. SCHEDULE 6.6.2(g) attached hereto contains examples of how Net Sales of Products from different countries at different royalty rates will be [***].

6.7. **Reverse Royalty Payments to Biogen Idec for a Discontinued Product**.

6.7.1. **Reverse Royalty for a Discontinued Product**. If Isis or any of its Affiliates or Sublicensees Commercializes a Discontinued Product for which Biogen Idec has paid Isis the license fee under Section 6.3, then following the First Commercial Sale of such Discontinued Product by Isis or its Affiliates or Sublicensees, Isis will pay Biogen Idec or its designated Affiliate a royalty of [***]% of Annual worldwide Net Sales of such Discontinued Product ("***Reverse Royalties***"). Isis' obligation to pay Biogen Idec Reverse Royalties will [***].

6.7.2. **Applicable Royalty Provisions**. In addition to this Section 6.7, the definition of Net Sales in APPENDIX 1 and the other provisions contained in this ARTICLE 6 governing payment of royalties from Biogen Idec to Isis will govern the payment of Reverse Royalties from Isis to Biogen Idec under this Section 6.7, *mutatis mutandis*, including the provisions of Sections 6.6.2, 6.8, 6.9, 6.10, 6.11, and 6.12.

6.8. **Third Party Payment Obligations**.

6.8.1. **Existing Isis In-License Agreements**.

(a) Certain of the Licensed Technology Controlled by Isis as of the Effective Date licensed to Biogen Idec under Section 4.1.1 are in-licensed or were acquired by Isis under the agreements with Third Party licensors or sellers listed on SCHEDULE 6.8.1 (such license or purchase agreements being the "***Isis In-License Agreements***"), and certain milestone or royalty payments and license maintenance fees may become payable by Isis to such Third Parties under the Isis In-License Agreements based on the Development and Commercialization of a Product by Biogen Idec under this Agreement.

(b) Any payment obligations arising under the Isis In-License Agreements as they apply to Products will be paid by [***] as [***].

6.8.2. **New In-Licensed Isis Product-Specific Patents; Isis Manufacturing and Analytical Patents**. If, after the Effective Date, Isis obtains Third Party Patent Rights necessary or useful to Develop, Manufacture or Commercialize a Product that would have been considered an Isis Product-Specific Patent had Isis Controlled such Patent Rights on the Effective Date, to the extent Controlled by Isis, Isis will include such Third Party Patent Rights in the license granted to Biogen Idec under Section 4.1.1 if Biogen Idec agrees in writing to pay Isis as [***].

6.8.3. **Additional Core IP In-License Agreements**.

(a) Biogen Idec will promptly provide Isis written notice of any Additional Core IP Biogen Idec believes it has identified and Isis will have the first right, but not the obligation, to negotiate with, and obtain a license from the Third Party Controlling such Additional Core IP. If Isis obtains such a Third Party license, Isis will include such Additional Core IP in the license granted to Biogen Idec under Section 4.1.1, and any financial obligations under such Third Party agreement will be paid solely by [***] as [***].

(b) If, however, Isis elects not to obtain such a license to such Third Party intellectual property, Isis will so notify Biogen Idec, and Biogen Idec may obtain such a Third Party license and, subject to Section 6.6.2(d)(ii), Biogen Idec may offset an amount equal to [***]% of any [***] paid by Biogen Idec under such Third Party license against any [***] of this Agreement in such country for [***].

(c) If it is unclear whether certain intellectual property identified by Biogen Idec pursuant to Section 6.8.3(a) is Additional Core IP under Section 6.8.3(b), Isis will send written notice to such effect to Biogen Idec, and the Parties will engage a mutually agreed upon independent Third Party intellectual property lawyer with expertise in the patenting of ASOs, and appropriate professional credentials in the relevant jurisdiction, to determine the question of whether or not such Third Party intellectual

property is Additional Core IP. The determination of the Third Party expert engaged under the preceding sentence will be binding on the Parties solely for purposes of determining whether Biogen Idec is permitted to [***]. The costs of any Third Party expert engaged under this Section 6.8.3(c) will be paid by the Party against whose position the Third Party lawyer's determination is made.

(d) Notwithstanding the determination of the Third Party lawyer under Section 6.8.3(c), if a Third Party Controlling Additional Core IP is awarded a judgment from a court of competent jurisdiction arising from its claim against Biogen Idec asserting that [***], Biogen Idec will be permitted to [***].

6.8.4. **Other Third Party Payments**.

(a) **Isis' Third Party Agreements**. Except as otherwise expressly agreed to by Biogen Idec under Section 6.8.2, after Option exercise, Biogen Idec will be responsible for paying [***]% of the [***] arising under any Third Party agreements entered into by Isis where either [***].

(b) **Biogen Idec's Third Party Agreements**. Without limiting any applicable [***] under Section 6.8.3(b), Biogen Idec will be responsible for paying [***]% of the [***] arising under any Third Party agreements entered into by Biogen Idec as they apply to Products.

6.9. **Payments**.

6.9.1. **Commencement**. Beginning with the Calendar Quarter in which the First Commercial Sale for a Product is made and for each Calendar Quarter thereafter, Biogen Idec will make royalty payments to Isis under this Agreement within [***] following the end of each such Calendar Quarter. Each royalty payment will be accompanied by a report, summarizing Net Sales for Products during the relevant Calendar Quarter and the calculation of royalties due thereon, including country, units, sales price and the exchange rate used. If no royalties are payable in respect of a given Calendar Quarter, Biogen Idec will submit a written royalty report to Isis so indicating together with an explanation as to why no such royalties are payable. In addition, beginning with the Calendar Quarter in which the First Commercial Sale for a Product is made and for each Calendar Quarter thereafter, within [***] following the end of each such Calendar Quarter, Biogen Idec will provide Isis a [***] report estimating the total Net Sales of, and royalties payable to Isis for, Products projected for such Calendar Quarter.

6.9.2. **Mode of Payment**. All payments under this Agreement will be (i) payable in full in U.S. dollars, regardless of the country(ies) in which sales are made, (ii) made by wire transfer of immediately available funds to an account designated by Isis in writing, and (iii) non-creditable [***], irrevocable and non-refundable. Whenever for the purposes of calculating the royalties payable under this

Agreement conversion from any foreign currency will be required, all amounts will first be calculated in the currency of sale and then converted into United States dollars by applying the monthly average rate of exchange calculated by using the foreign exchange rates

published in Bloomberg during the applicable month starting two Business Days before the beginning of such month and ending two Business Days before the end of such month as utilized by Biogen Idec, in accordance with generally accepted accounting principles, fairly applied and as employed on a consistent basis throughout Biogen Idec's operations.

6.9.3. **Records Retention**. Commencing with the First Commercial Sale of a Product, Biogen Idec will keep complete and accurate records pertaining to the sale of Products for a period of [***] after the year in which such sales occurred, and in sufficient detail to permit Isis to confirm the accuracy of the Net Sales or royalties paid by Biogen Idec hereunder.

6.10. **Audits**. After Option exercise, during the Agreement Term and for a period of [***] thereafter, at the request and expense of Isis, Biogen Idec will permit an independent certified public accountant of nationally recognized standing appointed by Isis, at reasonable times and upon reasonable notice, but in no case more than [***], to examine such records as may be necessary for the purpose of verifying the calculation and reporting of Net Sales and the correctness of any royalty payment made under this Agreement for any period within the preceding [***]. As a condition to examining any records of Biogen Idec, such auditor will sign a nondisclosure agreement reasonably acceptable to Biogen Idec in form and substance. Any and all records of Biogen Idec examined by such independent certified public accountant will be deemed Biogen Idec's Confidential Information. Upon completion of the audit, the accounting firm will provide both Biogen Idec and Isis with a written report disclosing whether the royalty payments made by Biogen Idec are correct or incorrect and the specific details concerning any discrepancies ("***Audit Report***"). If, as a result of any inspection of the books and records of Biogen Idec, it is shown that Biogen Idec's payments under this Agreement were less than the royalty amount which should have been paid, then Biogen Idec will make all payments required to be made by paying Isis the difference between such amounts to eliminate any discrepancy revealed by said inspection within 45 days of receiving the Audit Report, with interest calculated in accordance with Section 6.12. If, as a result of any inspection of the books and records of Biogen Idec, it is shown that Biogen Idec's payments under this Agreement were greater than the royalty amount which should have been paid, then [***]; *provided*, *however*, that if [***]. Isis will pay for such audit, except that if Biogen Idec is found to have underpaid Isis by more than [***] of the amount that should have been paid, Biogen Idec will reimburse Isis' reasonable costs of the audit.

6.11. **Taxes**.

6.11.1. **Taxes on Income**. Each Party will be solely responsible for the payment of all taxes imposed on its share of income arising directly or indirectly from the activities of the Parties under this Agreement.

6.11.2. **Withholding Tax**. The Parties agree to cooperate with one another and use reasonable efforts to lawfully avoid or reduce tax withholding or similar obligations in respect of royalties, milestone payments, and other payments made by the paying Party to the receiving Party under this Agreement. To the extent the paying Party is required to deduct and withhold taxes on any payment, the paying Party will pay the amounts of such taxes to the proper governmental authority for the account of the receiving Party and remit the net amount to the receiving Party in a timely manner. The paying Party will promptly furnish the receiving Party with proof of payment of such taxes. If documentation is necessary in order to secure an exemption from, or a reduction in, any withholding taxes, the Parties will provide such documentation to the extent they are entitled to do so.

6.11.3. **Tax Cooperation**. Isis will provide Biogen Idec with any and all tax forms that may be reasonably necessary in order for Biogen Idec to lawfully not withhold tax or to withhold tax at a reduced rate under an applicable bilateral income tax treaty. Following Biogen Idec's timely receipt of such tax forms from Isis, Biogen Idec will not withhold tax or will withhold tax at a reduced rate under an applicable bilateral income tax treaty, if appropriate under the applicable laws. Isis will provide any such tax forms to Biogen Idec upon request and in advance of the due date. Each Party will provide the other with reasonable assistance to enable the recovery, as permitted by applicable law, of withholding taxes resulting from payments made under this Agreement, such recovery to be for the benefit of the Party who would have been entitled to receive the money but for the application of withholding tax under this Section 6.11.

The provisions of this Section 6.11 are to be read in conjunction with the provisions of Section 12.4 below.

6.12. **Interest**. Any undisputed payments to be made hereunder that are not paid on or before the date such payments are due under this Agreement will bear interest at a rate per annum equal to the lesser of (i) the rate announced by Bank of America (or its successor) as its prime rate in effect on the date that such payment would have been first due plus 1% or (ii) the maximum rate permissible under applicable law.

ARTICLE 7.
INTELLECTUAL PROPERTY

7.1. **Ownership**.

7.1.1. **Isis Technology and Biogen Idec Technology**. As between the Parties, Isis will own and retain all of its rights, title and interest in and to the Licensed Know-How and Licensed Patents and Biogen Idec will own and retain all of its rights, title and interest in and to the Biogen Idec Know-How and Biogen Idec Patents, subject to any assignments, rights or licenses expressly granted by one Party to the other Party under this Agreement.

7.1.2. **Agreement Technology**. As between the Parties, Biogen Idec is the sole owner of any Know-How discovered, developed, invented or created solely by or on behalf of Biogen Idec or its Affiliates under this Agreement ("***Biogen Idec Program Know-How***") and any Patent Rights that claim or cover Biogen Idec Program Know-How ("***Biogen Idec Program Patents***" and together with the Biogen Idec Program Know-How, the "***Biogen Idec Program Technology***"), and will retain all of its rights, title and interest thereto, subject to any rights or licenses expressly granted by Biogen Idec to Isis under this Agreement. As between the Parties, Isis is the sole owner of any Know-How discovered, developed, invented or created solely by or on behalf of Isis or its Affiliates ("***Isis Program Know-How***") and any Patent Rights that claim or cover such Know-How ("***Isis Program Patents***"), and will retain all of its rights, title and interest thereto, subject to any

assignment, rights or licenses expressly granted by Isis to Biogen Idec under this Agreement. Any Know-How discovered, developed, invented or created jointly under this Agreement by or on behalf of both Parties or their respective Affiliates or Third Parties acting on their behalf ("***Jointly-Owned Program Know-How***"), and any Patent Rights that claim or cover such Jointly-Owned Program Know-How ("***Jointly-Owned Program Patents***", and together with the Jointly-Owned Program Know-How, the "***Jointly-Owned Program Technology***"), are owned jointly by Biogen Idec and Isis on an equal and undivided basis, including all rights, title and interest thereto, subject to any rights or licenses expressly granted by one Party to the other Party under this Agreement. Except as expressly provided in this Agreement, neither Party will have any obligation to account to the other for profits with respect to, or to obtain any consent of the other Party to license or exploit, Jointly-Owned Program Technology by reason of joint ownership thereof, and each Party hereby waives any right it may have under the laws of any jurisdiction to require any such consent or accounting. Each Party will promptly disclose to the other Party in writing, and will cause its Affiliates to so disclose, the discovery, development, invention or creation of any Jointly-Owned Program Technology. The Biogen Idec Program Patents, Isis Program Patents and Jointly-Owned Program Patents are collectively referred to herein as the "***Program Patents***."

7.1.3. **Joint Patent Committee**.

(a) The Parties will establish a "***Joint Patent Committee***" or "***JPC***." The JPC will serve as the primary contact and forum for discussion between the Parties with respect to intellectual property matters arising under this Agreement, and will cooperate with respect to the activities set forth in

this ARTICLE 7. Isis' obligation to participate in the JPC will terminate upon Biogen Idec's exercise of the Option. Thereafter, Isis will have the right, but not the obligation, to participate in JPC meetings. A strategy will be discussed with regard to intellectual property considerations when selecting a Development Candidate, prosecution and maintenance, defense and enforcement of Isis Product-Specific Patents that would be or are licensed to Biogen Idec under Section 4.1.1 in connection with the Product and Biogen Idec Product-Specific Patents, defense against allegations of infringement of Third Party Patent Rights, and licenses to Third Party Patent Rights or Know-How, in each case to the extent such matter would be reasonably likely to have a material impact on the Agreement or the licenses granted hereunder, which strategy will be considered in good faith by the Party entitled to designate a Development Candidate or prosecute, enforce and defend such Patent Rights, as applicable, hereunder, but will not be binding on such Party.

(b) Isis will provide the Joint Patent Committee with notice of any Know-How or Patent Rights discovered, developed, invented or created jointly by Isis and a Third Party in the performance of activities under the ISIS-DMPK$_{Rx}$ R&D Plan or solely by a Third Party performing activities under the ISIS-DMPK$_{Rx}$ R&D Plan on Isis' behalf (such Know-How and Patents, the "***Collaborator IP***") promptly after Isis receives notice or otherwise becomes aware of the existence of such Collaborator IP. The JPC will determine whether any such Collaborator IP would be infringed by the Development, registration, Manufacture or Commercialization of the Development Candidate or any Compound under consideration by Isis for potential designation as the Development Candidate. If the JPC (or independent patent counsel engaged pursuant to this Section 7.1.3(b)) determines that any Collaborator IP would be infringed by such Development, registration, Manufacture or Commercialization, [***]. In case of a dispute in the Joint Patent Committee over whether any Collaborator IP would be infringed by the Development, registration, Manufacture or Commercialization of the Development Candidate or any Compound under consideration by Isis for potential designation as the Development Candidate, at Biogen Idec's request, such dispute will be resolved by independent patent counsel not engaged or regularly employed in the past two years by either Party and reasonably acceptable to both Parties, taking into account any existing prior art. The decision of such independent patent counsel will be binding on the Parties. Expenses of such patent counsel will be borne by Biogen Idec.

(c) In addition, the Joint Patent Committee will be responsible for the determination of inventorship of Program Patents in accordance with United States patent laws. In case of a dispute in the Joint Patent Committee (or otherwise between Isis and Biogen Idec) over inventorship of Program Patents, if the Joint Patent Committee cannot resolve such

dispute, even after seeking the JSC's input, such dispute will be resolved by independent patent counsel not engaged or regularly employed in the past two years by either Party and reasonably acceptable to both Parties. The decision of such independent patent counsel will be binding on the Parties. Expenses of such patent counsel will be shared equally by the Parties.

(d) The JPC will comprise an equal number of members from each Party. The Joint Patent Committee will meet as often as agreed by them (and at least semi-Annually), to discuss matters arising out of the activities set forth in this ARTICLE 7. The JPC will determine by unanimous consent the JPC operating procedures at its first meeting, including the JPC's policies for replacement of JPC members, and the location of meetings, which will be codified in the written minutes of the first JPC meeting. To the extent reasonably requested by either Party, the Joint Patent Committee will solicit the involvement of more senior members of their respective legal departments (up to the most senior intellectual property attorney, where appropriate) with respect to critical issues, and may escalate issues to the Executives for input and resolution pursuant to Section 12.1. Each Party's representatives on the Joint Patent Committee will consider comments and suggestions made by the other in good faith. If either Party deems it reasonably advisable, the Parties will enter into a mutually agreeable common interest agreement covering the matters contemplated by this Agreement.

7.2. **Prosecution and Maintenance of Patents**.

7.2.1. **Patent Filings**. The Party responsible for Prosecution and Maintenance of any Patent Rights as set forth in Section 7.2.2 and Section 7.2.3 will endeavor to obtain patent protection for the Product as it Prosecutes and Maintains its other patents Covering products in development, using counsel of its own choice but reasonably acceptable to the other Party, in such countries as the responsible Party sees fit. Until the

earlier of Biogen Idec's exercise of the Option and the expiration or termination of the Option, Isis will use Commercially Reasonable Efforts to diligently Prosecute and Maintain all Isis Product-Specific Patents and any Jointly-Owned Program Patents Covering Products, in each case to the extent that Isis has the right to Prosecute and Maintain such Patent Rights.

7.2.2. Licensed Patents and Biogen Idec Patents.

(a) **Licensed Patents In General**. Prior to exercise of the Option, Isis will control and be responsible for all aspects of the Prosecution and Maintenance of all Licensed Patents, subject to Section 7.2.2(b), Section 7.2.3 and Section 7.2.4. During the Agreement Term, Isis will control and be responsible for all aspects of the Isis Core Technology Patents and Isis Manufacturing and Analytical Patents.

(b) **Licensed Patents After Option Exercise**. After Isis assigns to Biogen Idec or one or more designated Affiliates Isis' ownership interest in (i) all Isis Product-Specific Patents that are owned (whether solely owned or jointly owned with one or more Third Parties) by Isis, and (ii) any Jointly-Owned Program Patents Covering Products in accordance with Section 4.2, Biogen Idec will control and be responsible for all aspects of the Prosecution and Maintenance of all Isis Product-Specific Patents and Jointly-Owned Program Patents to the same extent Isis had the right to control and was responsible for such Prosecution and Maintenance immediately prior to such assignment, subject to Section 7.2.3 and Section 7.2.4, and will grant Isis the license set forth in Section 4.2.2.

(c) **Biogen Idec Patents**. Biogen Idec will control and be responsible for all aspects of the Prosecution and Maintenance of all Biogen Idec Patents, subject to Section 7.2.3 and Section 7.2.4.

7.2.3. Jointly-Owned Program Patents. Isis will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Program Patents that do not Cover Products. Prior to exercise of the Option, Isis will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Program Patents that Cover Products. After exercise of the Option, Biogen Idec will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Program Patents that Cover Products.

7.2.4. Other Matters Pertaining to Prosecution and Maintenance of Patents.

(a) Each Party will keep the other Party informed through the Joint Patent Committee as to material developments with respect to the Prosecution and Maintenance of the Isis Core Technology Patents set forth on Schedule 8.2.5(a), together with all Product-Specific Patents or Jointly-Owned Program Patents for which such Party has responsibility for Prosecution and Maintenance pursuant to Section 7.2.2, Section 7.2.3 or this Section 7.2.4, including by providing copies of material data as it arises, any office actions or office action responses or other correspondence that such Party provides to or receives from any patent office, including notice of all interferences, reissues, re-examinations, oppositions or requests for patent term extensions, and all patent-related filings, and by providing the other Party the timely opportunity to have reasonable input into the strategic aspects of such Prosecution and Maintenance.

(b) If Biogen Idec elects (a) not to file and prosecute patent applications for the Jointly-Owned Program Patent Rights or Isis Product-Specific Patents that have been licensed or assigned to Biogen Idec under this Agreement or the Biogen Idec Product-Specific Patents ("***Biogen Idec-Prosecuted Patents***") in a particular country, (b) not to continue the prosecution (including any interferences, oppositions, reissue proceedings, re-examinations,

and patent term extensions, adjustments, and restorations) or maintenance of any Biogen-Prosecuted Patent in a particular country, or (c) not to file and prosecute patent applications for the Biogen Idec-Prosecuted Patent in a particular country following a written request from Isis to file and prosecute in such country, then Biogen Idec will so notify Isis promptly in writing of its intention (including a reasonably detailed rationale for doing so) in good time to enable Isis to meet any deadlines by which an action must be taken to establish or preserve any such Patent Right in such country; and except as set forth in Section 7.2.4(c) Isis will have the right, but not the obligation, to file, prosecute, maintain, enforce, or otherwise pursue such Biogen Idec-Prosecuted Patent in the applicable country at its own expense with counsel of its own choice. In such case, Biogen Idec will cooperate with Isis to file for, or continue to Prosecute and Maintain or enforce, or otherwise pursue such Biogen-Prosecuted Patent in such country in Isis' own name, but only to the extent that Biogen Idec is not required to take any position with respect to such abandoned Biogen Idec-Prosecuted Patent that would be reasonably likely to adversely affect the scope, validity or enforceability of any of the other Patent Rights being prosecuted and maintained by Biogen Idec under this Agreement. Notwithstanding anything to the contrary in this Agreement, if Isis assumes responsibility for the Prosecution and Maintenance of any such Biogen Idec-Prosecuted Patent under this Section 7.2.4(b), Isis will have no obligation to notify Biogen Idec if Isis intends to abandon such Biogen Idec-Prosecuted Patent.

(c) Notwithstanding Section 7.2.4(b) above, if, after having consulted with outside counsel, Biogen Idec reasonably determines that filing or continuing to prosecute a patent application in a particular country for a Biogen Idec Prosecuted Patent (the ***"Conflicting Patent Right"***) is reasonably likely to adversely affect the scope, validity or enforceability of a patent application or issued patent in a particular country for another Biogen Idec Prosecuted Patent (the ***"Superior Patent Right"***), in each case where both the Conflicting Patent Right and the Superior Patent Right if issued would meet the criteria set forth in clause (i) of Section 6.6.2(a), then *so long as* Biogen Idec continues to Prosecute and Maintain the Superior Patent Right in accordance with this Agreement, Isis will not have the right under Section 7.2.4(b) above to file or prosecute the Conflicting Patent Right.

(d) If, during the Agreement Term, Isis intends to abandon any Isis Product-Specific Patent for which Isis is responsible for Prosecution and Maintenance without first filing a continuation or substitution, then, if the Option Deadline has not passed, Isis

will notify Biogen Idec of such intention at least 60 days before such Patent Right will become abandoned, and Biogen Idec will have the right, but not the obligation, to assume responsibility for the Prosecution and Maintenance thereof at its

own expense (subject to Section 7.3.1) with counsel of its own choice. Notwithstanding anything to the contrary in this Agreement, if Biogen Idec assumes responsibility for the Prosecution and Maintenance of any such Isis Product-Specific Patent under this Section 7.2.4(d), Biogen Idec will have no obligation to notify Isis if Biogen Idec intends to abandon such Isis Product-Specific Patent.

(e) The Parties, through the Joint Patent Committee, will cooperate in good faith to determine if and when any divisional or continuation applications will be filed with respect to any Program Patents or Product-Specific Patents, and where a divisional or continuation patent application filing would be practical and reasonable, then such a divisional or continuation filing will be made.

(f) If the Party responsible for Prosecution and Maintenance pursuant to Section 7.2.3 intends to abandon such Jointly-Owned Program Patent without first filing a continuation or substitution, then such Party will notify the other Party of such intention at least 60 days before such Jointly-Owned Program Patent will become abandoned, and such other Party will have the right, but not the obligation, to assume responsibility for the Prosecution and Maintenance thereof at its own expense (subject to Section 7.3.1) with counsel of its own choice, in which case the abandoning Party will, and will cause its Affiliates to, assign to the other Party (or, if such assignment is not possible, grant a fully-paid exclusive license in) all of their rights, title and interest in and to such Jointly-Owned Program Patents. If a Party assumes responsibility for the Prosecution and Maintenance of any such Jointly-Owned Program Patents under this Section 7.2.4(f), such Party will have no obligation to notify the other Party of any intention of such Party to abandon such Jointly-Owned Program Patents.

(g) In addition, the Parties will consult, through the Joint Patent Committee, and take into consideration the comments of the other Party for all matters relating to interferences, reissues, re-examinations and oppositions with respect to those Patent Rights in which such other Party (i) has an ownership interest, (ii) has received a license thereunder in accordance with this Agreement, or (iii) may in the future, in accordance with this Agreement, obtain a license or sublicense thereunder.

7.3. Patent Costs.

7.3.1. Jointly-Owned Program Patents. Unless the Parties agree otherwise, Isis and Biogen Idec will share equally the Patent Costs associated with the Prosecution and Maintenance of Jointly-Owned Program Patents; *provided that*, either Party may decline to pay its share of costs for filing, prosecuting and maintaining any Jointly-Owned Program Patents in a particular country or particular countries, in which case the declining Party will, and will cause its Affiliates to, assign to the other Party (or, if such assignment is not possible, grant a fully-paid exclusive license in) all of their rights, titles and interests in and to such Jointly-Owned Program Patents.

7.3.2. Licensed Patents and Biogen Idec Patents. Except as set forth in Section 7.2.4 and Section 7.3.1, each Party will be responsible for all Patent Costs incurred by such Party prior to and after the Effective Date in all countries in the Prosecution and Maintenance of Patent Rights for which such Party is responsible under Section 7.2; *provided, however*, that after Option exercise, Biogen Idec will be solely responsible for Patent Costs arising from the Prosecution and Maintenance of the Isis Product-Specific Patents.

7.4. Defense of Claims Brought by Third Parties.

7.4.1. If a Third Party initiates a Proceeding claiming a Patent Right owned by or licensed to such Third Party is infringed by the Development, Manufacture or Commercialization of the Product, (a) Isis will have the first right, but not the obligation, to defend against any such Proceeding initiated prior to Option exercise at its sole cost and expense and (b) Biogen Idec will have the first right, but not the obligation, to defend against any such Proceeding initiated after Option exercise at its sole cost and expense. If the Party having the first right to defend against such Proceeding (the "***Lead Party***") elects to defend against such Proceeding, then the Lead Party will have the sole right to direct the defense and to elect whether to settle such claim (but only with the prior written consent of the other Party, not to be unreasonably withheld, conditioned or delayed). The other Party will reasonably assist the Lead Party in defending such Proceeding and cooperate in any such litigation at the request and expense of the Lead Party. The Lead Party will provide the other Party with prompt written notice of the commencement of any such Proceeding that is of the type described in this Section 7.4, and the Lead Party will keep the other Party apprised of the progress of such Proceeding. If the Lead Party elects not to defend against a Proceeding, then the Lead Party will so notify the other Party in writing within 60 days after the Lead Party first receives written notice of the initiation of such Proceeding, and the other Party (the "***Step-In Party***") will have the right, but not the obligation, to defend against such Proceeding at its sole cost and expense and thereafter the Step-In Party will have the sole right to direct the defense thereof, including the right to settle such claim. In any event, the Party not defending such Proceeding will reasonably assist the other Party and cooperate in any such litigation at the request and expense of the Party defending such Proceeding. Each Party may at its own expense and with its own counsel join any defense initiated or directed by the other Party under this Section 7.4. Each Party will provide the other Party with prompt written notice of the commencement of any such Proceeding under this Section 7.4, and such Party will promptly furnish the other Party with a copy of each communication relating to the alleged infringement that is received by such Party.

7.4.2. Discontinued Product. If a Third Party initiates a Proceeding claiming that any Patent Right or Know-How owned by or licensed to such Third Party is infringed by the Development, Manufacture or Commercialization of a Discontinued Product, Isis will have the first right, but

not the obligation, to defend against and settle such Proceeding at its sole cost and expense. Biogen Idec will reasonably assist Isis in defending such Proceeding and cooperate in any such litigation at the request and expense of Isis. Each Party may at its own expense and with its own counsel join any defense directed by the other Party. Isis will provide Biogen Idec with prompt written notice of the commencement of any such Proceeding, or of any allegation of infringement of which Isis becomes aware and that is of the type described in this Section 7.4.2, and Isis will promptly furnish Biogen Idec with a copy of each communication relating to the alleged infringement received by Isis.

7.4.3. **Interplay Between Enforcement of IP and Defense of Third Party Claims**. Notwithstanding the provisions of Section 7.4.1 and Section 7.4.2, to the extent that a Party's defense against a Third Party claim of infringement under this Section 7.4 involves (i) the enforcement of the other Party's Know-How or Patent Rights, or (ii) the defense of an invalidity claim with respect to such other Party's Know-How or Patent Rights, then, in each case, the general concepts of Section 7.5 will apply to the enforcement of such other Party's Know-How or Patent Rights or the defense of such invalidity claim (*i.e.*, each Party has the right to enforce its own intellectual property, except that the relevant Commercializing Party will have the initial right, to the extent provided in Section 7.5, to enforce such Know-How or Patent Rights or defend such invalidity claim, and the other Party will have a step-in right, to the extent provided in Section 7.5, to enforce such Know-How or Patent Rights or defend such invalidity claim).

7.5. **Enforcement of Patents Against Competitive Infringement**.

7.5.1. **Duty to Notify of Competitive Infringement**. If either Party learns of an infringement, unauthorized use, misappropriation or threatened infringement by a Third Party to which such Party does not owe any obligation of confidentiality with respect to any Product-Specific Patents by reason of the development, manufacture, use or commercialization of a product directed against the RNA that encodes DMPK in the Field ("***Competitive Infringement***"), such Party will promptly notify the other Party in writing and will provide such other Party with available evidence of such Competitive Infringement; *provided*, *however*, that for cases of Competitive Infringement under Section 7.5.7 below, such written notice will be given within 10 days.

7.5.2. **Prior to Option Exercise**. For any Competitive Infringement with respect to the Product occurring after the Effective Date but before Option exercise, Isis will have the first right, but not the obligation, to institute, prosecute, and control a Proceeding with respect thereto, by counsel of its own choice, and Biogen Idec will have the right to be represented in that action by counsel of its own choice at its own expense, *however*, Isis will have the sole right to control such litigation. Isis will provide Biogen Idec with prompt written notice of the commencement of

any such Proceeding, and Isis will keep Biogen Idec apprised of the progress of such Proceeding. If Isis fails to initiate a Proceeding within a period of 90 days after receipt of written notice of such Competitive Infringement (subject to a 90 day extension to conclude negotiations, which extension will apply only in the event that Isis has commenced good faith negotiations with an alleged infringer for elimination of such Competitive Infringement within such 90 day period), Biogen Idec will have the right to initiate and control a Proceeding with respect to such Competitive Infringement by counsel of its own choice; *provided that* Isis will have the right to be represented in any such action by counsel of its own choice at its own expense. Notwithstanding the foregoing, Isis will at all times have the sole right to institute, prosecute, and control any Proceeding under this Section 7.5.2 to the extent involving any Isis Core Technology Patents or Isis Manufacturing and Analytical Patents.

7.5.3. **Following Option Exercise**. For any Competitive Infringement with respect to the Product (except for a Discontinued Product) occurring after Option exercise, so long as part of such Proceeding Biogen Idec also enforces any Patent Rights Controlled by Biogen Idec (including any Isis Product-Specific Patents assigned by Isis to Biogen Idec under this Agreement) being infringed that Cover the Product, then Biogen Idec will have the first right, but not the obligation, to institute, prosecute, and control a Proceeding with respect thereto by counsel of its own choice at its own expense, and Isis will have the right, at its own expense, to be represented in that action by counsel of its own choice, *however,* Biogen Idec will have the right to control such litigation. If Biogen Idec fails to initiate a Proceeding within a period of 90 days after receipt of written notice of such Competitive Infringement (subject to a 90 day extension to conclude negotiations, if Biogen Idec has commenced good faith negotiations with an alleged infringer for elimination of such Competitive Infringement within such 90 day period), Isis will have the right to initiate and control a Proceeding with respect to such Competitive Infringement by counsel of its own choice, and Biogen Idec will have the right to be represented in any such action by counsel of its own choice at its own expense. Notwithstanding the foregoing, Isis will at all times have the sole right to institute, prosecute, and control any Proceeding under this Section 7.5.3 to the extent involving any Isis Core Technology Patents or Isis Manufacturing and Analytical Patents.

7.5.4. **Joinder**.

(a) If a Party initiates a Proceeding in accordance with this Section 7.5, the other Party agrees to be joined as a party plaintiff where necessary and to give the first Party reasonable assistance and authority to file and prosecute the Proceeding. Subject to Section 7.5.5, the costs and expenses of each Party incurred pursuant to this Section 7.5.4(a) will be borne by the Party initiating such Proceeding.

(b) If one Party initiates a Proceeding in accordance with this Section 7.5.4, the other Party may join such Proceeding as a party plaintiff where necessary for such other Party to seek lost profits with respect to such infringement.

7.5.5. **Share of Recoveries**. Any damages or other monetary awards recovered with respect to a Proceeding brought pursuant to this Section 7.5 will be shared as follows:

(a) the amount of such recovery will first be applied to the Parties' reasonable out-of-pocket costs incurred in connection with such Proceeding (which amounts will be allocated *pro rata* if insufficient to cover the totality of such expenses); then

(b) any remaining proceeds constituting direct or actual damages for acts of infringement occurring prior to Biogen Idec's exercise of the Option will be (i) [***]; or (ii) [***]; then

(c) any remaining proceeds constituting direct or actual damages for acts of infringement occurring after Biogen Idec's exercise of the Option [***]; then

(d) any remaining proceeds constituting punitive or treble damages will be allocated between the Parties as follows: the Party initiating the Proceeding will receive and retain [***]% of such proceeds and the other Party will receive and retain [***]% of such proceeds.

7.5.6. **Settlement**. Notwithstanding anything to the contrary under this ARTICLE 7, neither Party may enter a settlement, consent judgment or other voluntary final disposition of a suit under this ARTICLE 7 that disclaims, limits the scope of, admits the invalidity or unenforceability of, or grants a license, covenant not to sue or similar immunity under a Patent Right Controlled by the other Party without first obtaining the written consent of the Party that Controls the relevant Patent Right.

7.5.7. **35 USC 271(e)(2) Infringement**. Notwithstanding anything to the contrary in this Section 7.5, solely with respect to Licensed Patents that have not been assigned to Biogen Idec under this Agreement for a Competitive Infringement under 35 USC 271(e)(2), the time period set forth in Section 7.5.2 during which a Party will have the initial right to bring a Proceeding will be shortened to a total of 25 days, so that, to the extent the other Party has the right, pursuant to such Section to initiate a Proceeding if the first Party does not initiate a Proceeding, such other Party will have such right if the first Party does not initiate a Proceeding within 25 days after such first Party's receipt of written notice of such Competitive Infringement.

7.6. **Other Infringement**.

7.6.1. **Jointly-Owned Program Patents**. With respect to the infringement of a Jointly-Owned Program Patent which is not a Competitive Infringement, the Parties will cooperate in good faith to bring suit together against such infringing party or the Parties may decide to permit one Party to solely bring suit. Any damages or other monetary awards recovered with respect to a Proceeding brought pursuant to this Section 7.6.1 will be shared as follows: (i) the amount of such recovery will first be applied to the Parties' reasonable out-of-pocket costs incurred in connection with such Proceeding (which amounts will be allocated *pro rata* if insufficient to cover the totality of such expenses); (ii) any remaining proceeds constituting direct damages will be [***], and (iii) any remaining proceeds constituting punitive or treble damages will be allocated as follows: (A) if the Parties jointly initiate a Proceeding pursuant to this Section 7.6.1, [***]; and (B) if only one Party initiates the Proceeding pursuant to this Section 7.6.1, such Party will receive [***]% of such proceeds and the other Party will receive [***]% of such proceeds.

7.6.2. **Patents Solely Owned by Isis**. Isis will retain all rights to pursue an infringement of any Patent Right solely owned by Isis which is other than a Competitive Infringement and Isis will retain all recoveries with respect thereto.

7.6.3. **Patents Solely Owned by Biogen Idec**. Biogen Idec will retain all rights to pursue an infringement of any Patent Right solely owned by Biogen Idec which is other than a Competitive Infringement and Biogen Idec will retain all recoveries with respect thereto.

7.7. **Patent Listing**.

7.7.1. **Biogen Idec's Obligations**. Biogen Idec will promptly, accurately and completely list, with the applicable Regulatory Authorities during the Agreement Term, all applicable Patent Rights that Cover the Product. Prior to such listings, the Parties will meet, through the Joint Patent Committee, to evaluate and identify all applicable Patent Rights, and Biogen Idec will have the right to review, where reasonable, original records relating to any invention for which Patent Rights are being considered by the Joint Patent Committee for any such listing. Notwithstanding the preceding sentence, Biogen Idec will retain final decision-making authority as to the listing of all applicable Patent Rights for the Product that are not Isis Core Technology Patents or Isis Manufacturing and Analytical Patents, regardless of which Party owns such Patent Rights.

7.7.2. **Isis' Obligations**. Isis will promptly, accurately and completely list, with the applicable Regulatory Authorities during the Agreement Term, all applicable Patent Rights that Cover a Discontinued Product. Prior to such listings, the Parties will meet, through the Joint Patent Committee, to evaluate and identify all applicable Patent Rights, and Isis will have the right to review, where reasonable, original records relating to any invention for which Patent Rights are being considered by the Joint Patent Committee for any such listing. Notwithstanding the preceding sentence, Isis will retain final decision-making authority as to the listing of all applicable Patent Rights for such Discontinued Products, as applicable, regardless of which Party owns such Patent Rights.

7.8. **CREATE Act**. Notwithstanding anything to the contrary in this ARTICLE 7, neither Party will have the right to make an election under the CREATE Act when exercising its rights under this ARTICLE 7 without the prior written consent of the other Party, which will not be unreasonably withheld, conditioned or delayed. With respect to any such permitted election, the Parties will use reasonable efforts to cooperate and coordinate their activities with respect to any submissions, filings or other activities in support thereof. The Parties acknowledge and agree that this Agreement is a "*joint research agreement*" as defined in the CREATE Act.

7.9. **Obligations to Third Parties**. Notwithstanding any of the foregoing, each Party's rights and obligations with respect to Licensed Technology under this ARTICLE 7 will be subject to the Third Party rights and obligations under any (i) New Third Party License the restrictions and obligations of which Biogen Idec has agreed to under Section 6.8.2, (ii) Prior Agreements, and (iii) Isis In-License Agreements; *provided*, *however*, that, to the

extent that Isis has a non-transferable right to prosecute, maintain or enforce any Patent Rights licensed to Biogen Idec hereunder and, this Agreement purports to grant any such rights to Biogen Idec, Isis will act in such regard with respect to such Patent Rights at Biogen Idec's direction.

7.10. **Additional Right and Exceptions**. Notwithstanding any provision of this ARTICLE 7, Isis retains the sole right to Prosecute and Maintain Isis Core Technology Patents and Isis Manufacturing and Analytical Patents during the Agreement Term and to control any enforcement of Isis Core Technology Patents and Isis Manufacturing and Analytical Patents, and will take the lead on such enforcement solely to the extent that the scope or validity of any Patent Rights Controlled by Isis and Covering the Isis Core Technology Patents or Isis Manufacturing and Analytical Patents is at risk.

7.11. **Patent Term Extension.** The Parties will cooperate with each other in gaining patent term extension wherever applicable to the Product. After exercising the Option, Biogen Idec will determine which patents will be extended.

7.12. **No Challenge**. As a material inducement for Isis entering into this Agreement, Biogen Idec covenants to Isis that during the Agreement Term, solely with respect to rights to the Licensed Patents that are included in a license granted to Biogen Idec under Section 4.1.1, Biogen Idec, its Affiliates or Sublicensees will not, in the United States or any other country, (a) commence or otherwise voluntarily determine to participate in (other than as may be necessary or reasonably required to assert a cross-claim or a counter-claim or to respond to a court request or order or administrative law request or order) any action or proceeding, challenging or denying the enforceability or validity of any claim within an issued patent or patent application within such Licensed Patents, or (b) direct, support or actively assist any other Person (other than as may be necessary or reasonably required to assert a cross-claim or a counter-claim or to respond to a court request or order or administrative law request or order) in bringing or prosecuting any action or proceeding challenging or denying the validity of any claim within an issued patent or patent application within such Licensed Patents. For purposes of clarification and without limiting any other available remedies, if Biogen Idec takes any of the actions described in clause (a) or clause (b) of this Section 7.12, Biogen Idec will have materially breached this Agreement and Isis may terminate this Agreement under Section 10.2.4(b).

ARTICLE 8.
REPRESENTATIONS AND WARRANTIES

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

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

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

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

8.1.4. the execution, delivery and performance of this Agreement by such Party will not constitute a default under or conflict with any agreement, instrument or understanding, oral or written, to which it is a party or by which it is bound, or violate any law or regulation of any court, governmental body or administrative or other agency having jurisdiction over such Party;

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

8.1.6. it has not employed (and, to the best of its knowledge, has not used a contractor or consultant that has employed) and in the future will not employ (or, to the best of its knowledge, use any contractor or consultant that employs, provided that such Party may reasonably rely on a representation made by such contractor or consultant) any Person debarred by the FDA (or subject to a similar sanction of EMA or foreign equivalent), or any Person which is the subject of an FDA debarment investigation or proceeding (or similar proceeding of EMA or foreign equivalent), in the conduct of the Pre-Clinical Studies or Clinical Studies of the Product and its activities under the ISIS-DMPK$_{Rx}$ R&D Plan.

8.2. **Representations and Warranties of Isis**. Isis hereby represents and warrants to Biogen Idec, as of the Effective Date, that:

8.2.1. To the best of its knowledge and belief, there are no additional licenses (beyond those that would be granted to Biogen Idec under Section 4.1.1 upon the exercise of the Option for a Product arising under the ISIS-DMPK$_{Rx}$ R&D Plan) under any intellectual property owned or Controlled by Isis or its Affiliates as of the Effective Date that would be required in order for Biogen Idec to further Develop and Commercialize a Product.

8.2.2. The Licensed Technology existing as of the Effective Date constitutes all of the Patent Rights and Know-How Controlled by Isis as of the Effective Date that are necessary to Develop, Manufacture or Commercialize Compounds contemplated under the ISIS-DMPK$_{Rx}$ R&D Plan in the Field. Isis has not previously assigned, transferred, conveyed or otherwise encumbered its right, title and interest in the Licensed Technology in a manner that conflicts with any rights granted to Biogen Idec hereunder.

8.2.3. Neither Isis nor its Affiliates owns or Controls any Patent Rights or Know How covering formulation or delivery technology as of the Effective Date that would be useful or necessary in order for Biogen Idec to further Develop or Commercialize Compounds contemplated

under the ISIS-DMPK$_{Rx}$ R&D Plan.

8.2.4. There are no claims, judgments or settlements against or owed by Isis or its Affiliates or pending against Isis or, to the best of Isis' knowledge, threatened against Isis, in each case relating to the Isis Technology that could impact activities under this Agreement. To the best of Isis' knowledge, there are no claims, judgments or settlements against or owed by any Third Party that is party to a Prior Agreement, or pending or threatened claims or litigation against any Third Party that is party to a Prior Agreement, in each case relating to the Isis Technology that would impact activities under this Agreement.

8.2.5. SCHEDULE 8.2.5(a), SCHEDULE 8.2.5(b) and SCHEDULE 8.2.5(c) set forth true, correct and complete lists of all Isis Core Technology Patents, Isis Manufacturing and Analytical Patents, and Isis Product-Specific Patents that apply to the Compounds contemplated under the ISIS-DMPK$_{Rx}$ R&D Plan as of the Effective Date, respectively, and indicates whether each such Patent Right is owned by Isis or licensed by Isis from a Third Party and if so, identifies the licensor or sublicensor from which the Patent Right is licensed. Isis Controls such Patent Rights existing as of the Effective Date and is entitled to grant all rights and licenses (or sublicenses, as the case may be) under such Patent Rights it purports to grant to Biogen Idec under this Agreement.

8.2.6. At the Effective Date (a) there is no fact or circumstance known by Isis that would cause Isis to reasonably conclude that any Licensed Patent is invalid or un-enforceable, (b) there is no fact or circumstance known by Isis that would cause Isis to reasonably conclude the inventorship of each Licensed Patent is not

properly identified on each patent, (c) all official fees, maintenance fees and annuities for the Licensed Patents have been paid and all administrative procedures with governmental agencies have been completed, and (d) none of the Isis Product Specific Patents is currently involved in any interference, reissue, re-examination, cancellation or opposition proceeding and neither Isis, nor any of its Affiliates, has received any written notice from any person, or has knowledge, of such actual or threatened proceeding.

8.2.7. SCHEDULE 6.8.1 sets forth true, correct and complete lists of all Isis In-License Agreements relating to Licensed Technology necessary or useful to conduct the research, Development, Manufacture or Commercialization of Compounds as contemplated under the ISIS-DMPK$_{Rx}$ R&D Plan existing on the Effective Date. All Isis In-License Agreements are in full force and effect and have not been modified or amended. Neither Isis nor, to the best knowledge of Isis, the Third Party licensor in an Isis In-License Agreement is in default with respect to a material obligation under such Isis In-License Agreement, and neither such party has claimed or has grounds upon which to claim that the other party is in default with respect to a material obligation under, any Isis In-License Agreement.

8.2.8. SCHEDULE 8.2.8 is a complete and accurate list of all agreements that create Third Party Obligations that affect the rights granted by Isis to Biogen Idec under this Agreement.

8.2.9. To the best of Isis' knowledge, the Development, Manufacture (as manufactured by Isis at its facility as of the Effective Date) and Commercialization of Compounds as contemplated by the ISIS-DMPK$_{Rx}$ R&D Plan and this Agreement does not [***] or [***].

8.2.10. As of the Effective Date, Isis has no [***].

8.3. **Isis Covenants**. Isis hereby covenants to Biogen Idec that, except as expressly permitted under this Agreement:

8.3.1. Isis will promptly amend SCHEDULE 8.2.5(a), SCHEDULE 8.2.5(b) and SCHEDULE 8.2.5(c) and submit such amended Schedules to Biogen Idec if Isis becomes aware that any Isis Core Technology Patents, Isis Manufacturing and Analytical Patents or Isis Product-Specific Patents are not properly identified on such Schedule.

8.3.2. during the Agreement Term, Isis will maintain and not breach any Isis In-License Agreements and any agreements with Third Parties entered into after the Effective Date ("***New Third Party Licenses***") that provide a grant of rights from such Third Party to Isis that are Controlled by Isis and are licensed or may become subject to a license from Isis to Biogen Idec for the Development Candidate under this Agreement;

8.3.3. Isis will promptly notify Biogen Idec of any material breach by Isis or a Third Party of any New Third Party License, and in the event of a breach by Isis, will permit Biogen Idec to cure such breach on Isis' behalf upon Biogen Idec's request;

8.3.4. Isis will not amend, modify or terminate any Isis In-License Agreement or New Third Party License in a manner that would adversely affect Biogen Idec's rights hereunder without first obtaining Biogen Idec's written consent, which consent may be withheld in Biogen Idec's sole discretion;

8.3.5. Isis will not enter into any new agreement or other obligation with any Third Party, or amend an existing agreement with a Third Party, in each case that restricts, limits or encumbers the rights granted to Biogen Idec under this Agreement;

8.3.6. Isis will cause its Affiliates, licensees and sublicensees to comply with the terms of Section 2.1;

8.3.7. all employees and contractors of Isis performing Development activities hereunder on behalf of Isis will be obligated to assign all right, title and interest in and to any inventions developed by them, whether or not patentable, to Isis or such Affiliate, respectively, as the sole owner thereof; and

8.3.8. If, after the Effective Date, Isis becomes the owner or otherwise acquires Control of any formulation or delivery technology that would be necessary or useful in order for Biogen Idec to further Develop, Manufacture or Commercialize a Product, and Biogen Idec has exercised its

Option and the license granted to Biogen Idec under this Agreement is in effect, Isis will make such technology available to Biogen Idec on commercially reasonable terms.

8.4. **DISCLAIMER. EXCEPT AS OTHERWISE EXPRESSLY SET FORTH IN THIS AGREEMENT, NEITHER PARTY NOR ITS AFFILIATES MAKES ANY REPRESENTATION OR EXTENDS ANY WARRANTY OF ANY KIND, EITHER EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. BIOGEN IDEC AND ISIS UNDERSTAND THAT THE PRODUCT IS THE SUBJECT OF ONGOING RESEARCH AND DEVELOPMENT AND THAT NEITHER PARTY CAN ASSURE THE SAFETY, USEFULNESS OR COMMERCIAL OR TECHNICAL VIABILITY OF THE PRODUCT.**

ARTICLE 9.
INDEMNIFICATION; INSURANCE

9.1. **Indemnification by Biogen Idec**. Biogen Idec will indemnify, defend and hold harmless Isis and its Affiliates, and its or their respective directors, officers, employees and agents, from and against any and all liabilities, damages, losses, costs and expenses including the reasonable fees of attorneys (collectively "***Losses***") arising out of or resulting from any and all Third Party suits, claims, actions, proceedings or demands ("***Claims***") based upon:

9.1.1. the gross negligence or willful misconduct of Biogen Idec, its Affiliates or Sublicensees and its or their respective directors, officers, employees and agents, in connection with Biogen Idec's performance of its obligations or exercise of its rights under this Agreement;

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

9.1.3. the Development or Manufacturing activities that are conducted by or on behalf of Biogen Idec or its Affiliates or Sublicensees (which will exclude any Development or Manufacturing activities that are conducted by or on behalf of Isis pursuant to this Agreement); or

9.1.4. the Commercialization of the Product by or on behalf of Biogen Idec or its Affiliates or Sublicensees;

except, in each case above, to the extent such Claim arose out of or resulted from or is attributable to any acts or omissions of Isis or its Affiliates, licensees, Sublicensees or contractors, and its or their respective directors, officers, employees and agents or other circumstance for which Isis has an indemnity obligation pursuant to Section 9.2.

9.2. **Indemnification by Isis**. Isis will indemnify, defend and hold harmless Biogen Idec and its Affiliates, and its or their respective directors, officers, employees and agents, from and against any and all Losses arising out of or resulting from any and all Claims based upon:

9.2.1. the gross negligence or willful misconduct of Isis, its Affiliates or Sublicensees or its or their respective directors, officers, employees and agents, in connection with Isis' performance of its obligations or exercise of its rights under this Agreement;

9.2.2. any breach of any representation or warranty or express covenant made by Isis under ARTICLE 8 or any other provision under this Agreement;

9.2.3. any Development or Manufacturing activities that are conducted by or on behalf of Isis or its Affiliates or Sublicensees (which will exclude any Development or Manufacturing activities that are conducted by or on behalf of Biogen Idec pursuant to this Agreement); or

9.2.4. any development, manufacturing or commercialization activities that are conducted by or on behalf of Isis or its Affiliates or Sublicensees with respect to a Discontinued Product.

except, in each case above, to the extent such Claim arose out of or resulted from or is attributable to any acts or omissions of Biogen Idec or its Affiliates, licensees, Sublicensees or contractors and its or their respective directors, officers, employees and agents or other circumstance for which Biogen Idec has an indemnity obligation pursuant to Section 9.1.

9.3. **Procedure**. If a Person entitled to indemnification under Section 9.1 or Section 9.2 (an "***Indemnitee***") seeks such indemnification, such Indemnitee will (i) inform the indemnifying Party in writing of a Claim as soon as reasonably practicable after such Indemnitee receives notice of such Claim, (ii) permit the indemnifying Party to assume direction and control of the defense of the Claim (including the sole right to settle such Claim at the sole discretion of the indemnifying Party, *provided that* (A) such settlement or compromise does not admit any fault or negligence on the part of the Indemnitee, or impose any obligation on, or otherwise materially adversely affect, the Indemnitee or other Party and (B) the indemnifying Party first obtain the written consent of the Indemnitee with respect to such settlement, which consent will not be unreasonably withheld), (iii) cooperate as reasonably requested (at the expense of the indemnifying Party) in the defense of the Claim, and (iv) undertake reasonable steps to mitigate any Losses with respect to the Claim. The provisions of Section 7.4 will govern the procedures for responding to a Claim of infringement described therein. Notwithstanding anything in this Agreement to the contrary, the indemnifying Party will have no liability under Section 9.1 or Section 9.2, as the case may be, for Claims settled or compromised by the Indemnitee without the indemnifying Party's prior written consent.

9.4. **Insurance**.

9.4.1. **Isis' Insurance Obligations**. Isis will maintain, at its cost, reasonable insurance against liability and other risks associated with its activities contemplated by this Agreement, *provided, that*, at a minimum, Isis will maintain, in force from 30 days prior to enrollment of the first

patient in a Clinical Study, a [***] insurance policy providing coverage of at least $[***] per claim and $[***] Annual aggregate. Isis will furnish to Biogen Idec evidence of such insurance upon request.

9.4.2. **Biogen Idec's Insurance Obligations**. Biogen Idec will maintain, at its cost, reasonable insurance against liability and other risks associated with its activities contemplated by this Agreement, *provided*, *that*, at a minimum, Biogen Idec will maintain, in force from 30 days prior to enrollment of the first patient in a Clinical Study, a [***] insurance policy providing coverage of at least $[***] per claim and $[***] Annual aggregate and, *provided further* that such coverage is increased to at least $[***] at least 30 days before Biogen Idec initiates the First Commercial Sale of the Product hereunder. Biogen Idec will furnish to Isis evidence of such insurance upon request. Notwithstanding the foregoing, Biogen Idec may self-insure to the extent that it self-insures for its other products, but at a minimum will self-insure at levels that are consistent with levels customarily maintained against similar risks by similar companies in Biogen Idec's industry.

9.5. **LIMITATION OF CONSEQUENTIAL DAMAGES**. **EXCEPT FOR (a) CLAIMS OF A THIRD PARTY THAT ARE SUBJECT TO INDEMNIFICATION UNDER THIS ARTICLE 9, (b) CLAIMS ARISING OUT OF A PARTY'S WILLFUL MISCONDUCT OF THIS AGREEMENT, (c) A PARTY'S BREACH OF ARTICLE 2, OR A BREACH OF SECTION 10.4.3(a) BY BIOGEN IDEC OR ITS AFFILIATES OR (d) CLAIMS ARISING OUT OF A PARTY'S BREACH OF ITS CONFIDENTIALITY OBLIGATIONS UNDER THIS AGREEMENT, NEITHER PARTY NOR ANY OF ITS AFFILIATES WILL BE LIABLE TO THE OTHER PARTY TO THIS AGREEMENT OR ITS AFFILIATES FOR ANY INCIDENTAL, CONSEQUENTIAL, SPECIAL, PUNITIVE OR OTHER INDIRECT DAMAGES OR LOST OR IMPUTED PROFITS OR ROYALTIES, LOST DATA OR COST OF PROCUREMENT OF SUBSTITUTE GOODS OR SERVICES, WHETHER LIABILITY IS ASSERTED IN CONTRACT, TORT (INCLUDING NEGLIGENCE AND STRICT PRODUCT LIABILITY), INDEMNITY OR CONTRIBUTION, AND IRRESPECTIVE OF WHETHER THAT PARTY OR ANY REPRESENTATIVE OF THAT PARTY HAS BEEN ADVISED OF, OR OTHERWISE MIGHT HAVE ANTICIPATED THE POSSIBILITY OF, ANY SUCH LOSS OR DAMAGE.**

ARTICLE 10.
TERM; TERMINATION

10.1. **Agreement Term; Expiration**. This Agreement is effective as of the Effective Date and, unless earlier terminated pursuant to the other provisions of this ARTICLE 10, will continue in full force and effect until this Agreement expires as follows:

10.1.1. on a country-by-country basis, on the date of expiration of all payment obligations by the Commercializing Party under this Agreement with respect to the Product (or a Discontinued Product) in such country;

10.1.2. in its entirety upon the expiration of all payment obligations under this Agreement with respect to the Product (or a Discontinued Product) in all countries pursuant to Section 10.1.1; and

10.1.3. where Biogen Idec has not provided Isis a written notice stating Biogen Idec is exercising its Option and paid Isis the license fee under Section 6.3 by the Option Deadline.

The period from the Effective Date until the date of expiration of this Agreement pursuant to this Section 10.1 is the "***Agreement Term***."

10.2. **Termination of the Agreement**.

10.2.1. **Biogen Idec's Termination for Convenience**. At any time following payment by Biogen Idec of the upfront fee under Section 6.1, subject to Section 10.4.1 below, Biogen Idec will be entitled to terminate this Agreement for convenience by providing 90 days written notice to Isis of such termination.

10.2.2. **Termination for Failure to Divest Directly Competitive Product**. If a Competing Acquirer does not, during the Divestiture Period, divest itself of a Directly Competitive Product, terminate the development and commercialization of such Directly Competitive Product or assign this Agreement to a Third Party that is not itself developing or commercializing a Directly Competitive Product as set forth in Section 12.5, Biogen Idec may terminate this Agreement immediately upon providing written notice to Isis.

10.2.3. **Termination Due to Failure to Obtain HSR Clearance**.

(a) If the Parties make an HSR Filing under Section 3.1.4 of this Agreement and the HSR Clearance Date has not occurred on or prior to 90 days after the effective date of the latest HSR Filing made by the Parties, this Agreement will terminate (i) at the election of either Party immediately upon notice to the other Party, if the FTC or the DOJ has instituted (or threatened to institute) any action, suit or proceeding including seeking, threatening to seek or obtaining a preliminary injunction under the HSR Act against Biogen Idec and Isis to enjoin or otherwise prohibit the transactions contemplated by this Agreement, or (ii) at the election of either Party, immediately upon notice to the other Party, if the Parties have not resolved any and all objections of the FTC and DOJ as contemplated by Section 3.1.4(b). Notwithstanding the foregoing, this Section 10.2.3 will not apply if an HSR Filing is not required to fully perform this Agreement.

(b) If this Agreement is terminated in accordance with Section 10.2.3(a), then, *until* [***] as follows:

(i) If Isis [***]; and

(ii) If Isis, its Affiliates or the licensee [***].

Nothing in this Section 10.2.3(b) obligates Isis to (y) [***] or (z) [***].

10.2.4. Termination for Material Breach.

(a) **Biogen Idec's Right to Terminate**. If Biogen Idec believes that Isis is in material breach of this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under Section 1.3, which is governed by Section 10.2.5 below), then Biogen Idec may deliver notice

of such material breach to Isis. If the breach is curable, Isis will have 60 days to cure such breach. If Isis fails to cure such breach within the 60 day period, or if the breach is not subject to cure, Biogen Idec may terminate this Agreement by providing written notice to Isis. Without limiting the foregoing, breach by a Party of ARTICLE 2 of this Agreement constitutes a material breach of this Agreement.

(b) **Isis' Right to Terminate**. If Isis believes that Biogen Idec is in material breach of (i) a payment obligation under ARTICLE 6, (ii) Section 7.12, or (iii) one or more material provisions of this Agreement where such material breaches have occurred multiple times over the course of at least a 12-month period (where such material breach is not a single continuous event) demonstrating a pattern of failing to timely comply with Biogen Idec's obligations under this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under Section 5.1, which is governed by Section 10.2.5 below), then Isis may deliver notice of such material breach to Biogen Idec. If the breach is curable, Biogen Idec will have 60 days to cure such breach (except to the extent such breach involves the failure to make a payment when due, which breach must be cured within 30 days following such notice). If Biogen Idec fails to cure such breach within the 60 day or 30 day period, as applicable, or if the breach is not subject to cure, Isis may terminate this Agreement by providing written notice to Biogen Idec.

10.2.5. Remedies for Failure to Use Commercially Reasonable Efforts.

(a) If Isis, in Biogen Idec's reasonable determination, fails to use Commercially Reasonable Efforts in the activities contemplated in Section 1.3 prior to Option exercise, Biogen Idec will notify Isis and, within 30 days thereafter, Isis and Biogen Idec will meet and confer to discuss and resolve the matter in good faith, and attempt to devise a mutually agreeable plan to address any outstanding issues related to Isis' use of Commercially Reasonable Efforts in Section 1.3. Following such a meeting, if Isis fails to use Commercially Reasonable Efforts as contemplated by Section 1.3, then subject to Section 10.2.6 below, Biogen Idec will have the right, at its sole discretion, to (i) terminate this Agreement or, (ii) prior to Option exercise, Biogen Idec may elect to trigger the alternative remedy provisions of Section 10.3 below in lieu of terminating this Agreement by providing written notice to Isis. This Section 10.2.5(a) sets forth Biogen Idec's sole and exclusive remedies if Isis fails to use Commercially Reasonable Efforts in the activities contemplated in Section 1.3 prior to Option exercise.

(b) If Biogen Idec, in Isis' reasonable determination, fails to use Commercially Reasonable Efforts under Section 5.1 above, Isis will notify Biogen Idec and, within 30 days thereafter, Isis and Biogen Idec will meet and confer to discuss and resolve the matter in good faith, and attempt to

devise a mutually agreeable plan to address any outstanding issues related to Biogen Idec's use of Commercially Reasonable Efforts in Section 5.1. Following such a meeting, if Biogen Idec fails to use Commercially Reasonable Efforts as contemplated by Section 5.1, then subject to Section 10.2.6 below, Isis will have the right, at its sole discretion, to terminate this Agreement.

10.2.6. Disputes Regarding Material Breach. Notwithstanding the foregoing, if the Breaching Party in Section 10.2.4 or Section 10.2.5 disputes in good faith the existence, materiality, or failure to cure of any such breach which is not a payment breach, and provides notice to the Non-Breaching Party of such dispute within such 60 day period, the Non-Breaching Party will not have the right to terminate this Agreement in accordance with Section 10.2.4 or Section 10.2.5, or trigger the alternative remedy provisions of Section 10.2.5, as applicable, unless and until it has been determined in accordance with Section 12.1 that this Agreement was materially breached by the Breaching Party and the Breaching Party fails to cure such breach within 30 days following such determination. It is understood and acknowledged that during the pendency of such dispute, all the terms and conditions of this Agreement will remain in effect and the Parties will continue to perform all of their respective obligations hereunder, including satisfying any payment obligations.

10.2.7. Termination for Insolvency.

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

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

promptly delivered to the non-bankrupt Party, unless the bankrupt Party elects in writing to continue, and continues, to perform all of its obligations under this Agreement.

10.2.8. **Termination if Isis Cannot Identify a Development Candidate**. If, despite Isis' Commercially Reasonable Efforts, by [***], Isis has not designated at least one Development Candidate, then either Party may terminate this Agreement in its entirety by providing notice of such termination to the other Party on or before [***]; *provided, however*, that if at any time during the [***] period after such termination Isis' RMC designates an ASO discovered by Isis that is designed to bind to the RNA that encodes DMPK as a development candidate ready to start IND-Enabling Toxicology Studies (such ASO, a "***Post-Termination Development Candidate***"), then, Isis will notify Biogen Idec and will provide Biogen Idec with the data package presented to Isis' RMC to approve such Post-Termination Development Candidate. Biogen Idec will then have [***] from its receipt of such package to elect to enter into an agreement for an option and license under the same terms as the terms set forth in this Agreement (except that no additional upfront payment under Section 6.1 will be due). If, within [***] after Biogen Idec's receipt of such notice from Isis, Biogen Idec provides Isis with written notice that it accepts such offer from Isis for such Post-Termination Development Candidate, the Parties will execute an agreement regarding such Post-Termination Development Candidate containing the same terms as those described herein. If Biogen Idec either notifies Isis that it declines the offer for such Post-Termination Development Candidate, or Biogen Idec does not provide Isis with written notice during such [***] period that Biogen Idec accepts such offer from Isis for such Post-Termination Development Candidate, then Isis will be free to research, develop, manufacture and commercialize such Post-Termination Development Candidate (and/or any other ASO designed to bind to the RNA that encodes DMPK in the Field) by itself or with or for a Third Party.

10.3. **Alternative Remedies to Termination Available to Biogen Idec Prior to Option Exercise**. If, prior to Option exercise, Biogen Idec elects to (i) exercise the alternative remedy provisions of this Section 10.3 in lieu of terminating this Agreement by providing written notice of such election to Isis in accordance with Section 10.2.5(a), or (ii) exercise the Option in accordance with [***], then in each case this Agreement will continue in full force and effect with the following modifications:

(a) Isis will have no further rights or obligations to Develop the Product under the ISIS-DMPK$_{Rx}$ R&D Plan or participate in the JSC, JPC or any other subcommittees or working groups established pursuant to this Agreement, each of which will be disbanded. Biogen Idec will solely make all decisions that this Agreement would otherwise require or permit the JSC, JPC or any other subcommittees or working groups, or the Parties collectively, to make; *provided*, *however*, that Biogen Idec will not have the right to create any obligations or incur any liabilities for or on behalf of Isis;

(b) effective as of the date of Biogen Idec's notice to Isis electing the alternative remedy provisions of this Section 10.3, Biogen Idec will be deemed for all purposes of this Agreement to have exercised the Option;

(c) Biogen Idec will have and Isis grants, the exclusive license granted to Biogen Idec under Section 4.1.1;

(d) Biogen Idec may exclude Isis from all discussions with Regulatory Authorities regarding Products, except to the extent Isis' participation is required by a Regulatory Authority or is otherwise reasonably necessary to comply with Applicable Law;

(e) Biogen Idec's obligation to make further disclosures of Know-How or other information to Isis pursuant to this Agreement (including pursuant to Section 4.5 and Section 5.2.2) will terminate, other than reports required by Section 6.9.1, Section 10.4.3 (if applicable), and as reasonably required to permit Isis to perform its obligations under this Agreement;

(f) Isis will perform its obligations under Section 4.5 with respect to the Product within 60 days of Biogen Idec electing to exercise its alternative remedies under this Section 10.3 or exercising the Option in accordance with [***], and will provide to Biogen Idec and its Third Party contractors all Know-How, assistance, assignments and other support reasonably requested to assist Biogen Idec in assuming complete responsibility for the Development and Manufacture of the Products in an efficient and orderly manner; and

(g) the financial provisions of ARTICLE 6 will be modified as follows:

(i) [***] *Payments*. Biogen Idec will [***]; and

(ii) *License Fee*. The license fee set forth in Section 6.3 will be [***]. Such [***] will be due within 90 days after [***] and Biogen Idec's [***].

The milestone provisions of Section 6.4 and the royalty provisions of Section 6.6 will [***].

10.4. **Consequences of Expiration or Termination of the Agreement**.

10.4.1. **In General**. If this Agreement expires or is terminated by a Party in accordance with this ARTICLE 10 at any time and for any reason, the following terms will apply to any such expiration or termination:

(a) **Return of Information and Materials**. The Parties will return (or destroy, as directed by the other Party) all data, files, records and other materials containing or comprising the other Party's Confidential Information. Notwithstanding the foregoing, the Parties will be permitted to retain one copy of such data, files, records, and other materials for archival and legal compliance purposes.

(b) **Perpetual, Royalty-Free Non-Exclusive License**. If Biogen Idec has exercised its Option, then upon expiration of the Reduced Royalty Period in all countries in which Products are being or have been sold, Isis will and hereby does grant to Biogen Idec a perpetual, nonexclusive, worldwide, royalty-free, fully paid-up, sublicensable license under the Isis Know-How to Manufacture, Develop and Commercialize any Product.

(c) **Accrued Rights**. Termination or expiration of this Agreement for any reason will be without prejudice to any rights or financial compensation that will have accrued to the benefit of a Party prior to such termination or expiration. Such termination or expiration will not relieve a Party from obligations that are expressly indicated to survive the termination or expiration of this Agreement. For purposes of clarification, milestone payments under ARTICLE 6 accrue as of the date the applicable Milestone Event is achieved even if the payment is not due at that time.

(d) **Survival**. The following provisions of this Agreement will survive the expiration or termination of this Agreement: Section 4.1.2(b) (Effect of Termination on Sublicenses), Section 4.2.2, Section 4.5 (Technology Transfer after Option Exercise) (but only to the extent necessary to satisfy the requirements of Section 10.4.3), Section 6.7 (Reverse Royalty Payments to Biogen Idec for a Discontinued Product), Section 6.9.3 (Records Retention), Section 6.10 (Audits), Section 7.1.1 (Isis Technology and Biogen Idec Technology), Section 7.1.2 (Agreement Technology), Section 8.4 (Disclaimer), Section 9.1 (Indemnification by Biogen Idec), Section 9.2 (Indemnification by Isis), Section 9.3 (Procedure), Section 9.4.1 (Isis' Insurance Obligations), Section 9.4.2 (Biogen Idec's Insurance Obligations), Section 9.5 (Limitation of Consequential Damages), Section 10.2.3(b), Section 10.2.7 (Termination for Insolvency), Section 10.2.8, (Termination if Isis Cannot Identify a Development Candidate), Section 10.4 (Consequences of Expiration or Termination of the Agreement) (except Section 10.4.4 (Remedies Available to Biogen Idec for Isis' Material Breach After Option Exercise)), ARTICLE 11 (Confidentiality), ARTICLE 12 (Miscellaneous) and APPENDIX 1 (Definitions) (to the extent definitions are embodied in the foregoing listed Articles and Sections).

10.4.2. **Termination Before Option Exercise**. If this Agreement expires or is terminated by a Party in accordance with this ARTICLE 10 before Option exercise, then, in addition to the terms set forth in Section 10.4.1, the following terms will apply to any such expiration or termination:

(a) Biogen Idec's Option under Section 3.1 will expire and Isis will be free to Develop and Commercialize the Product (and any other Compounds) on its own or with a Third Party.

(b) Neither Party will have any further obligations under Section 2.1 of this Agreement.

(c) To the extent requested by Isis, Biogen Idec will promptly (1) assign to Isis any Manufacturing Agreements identified by Isis to which Biogen Idec is a party, and (2) transfer to Isis all data, results and information (including Biogen Idec's Confidential Information and any regulatory documentation (including drafts)) related to the testing and Clinical Studies under the ISIS-DMPK$_{Rx}$ R&D Plan in the possession of Biogen Idec and its contractors to the extent such data, results and information were generated by or on behalf of Biogen Idec under this Agreement; and Isis will pay all out-of-pocket direct Third Party costs and expenses in transferring such data, results and information together with Biogen Idec's FTE Cost in transferring such data, results and information.

(d) If this Agreement is terminated by Biogen Idec for convenience prior to Option exercise, Biogen Idec will [***].

(e) Except as explicitly set forth in Section 10.4.1(a), Section 10.4.1(c) or Section 10.4.1(d), Biogen Idec will have no further rights and Isis will have no further obligations with respect to the terminated ISIS-DMPK$_{Rx}$ R&D Plan.

10.4.3. **Termination After Option Exercise**. If this Agreement is terminated by a Party in accordance with this ARTICLE 10 after Option exercise, then, in addition to the terms set forth in Section 10.4.1, the following terms will apply to any such termination:

(a) The licenses granted by Isis to Biogen Idec under this Agreement will terminate and Biogen Idec, its Affiliates and Sublicensees will cease selling the Product.

(b) Neither Party will have any further obligations under Section 2.1 of this Agreement.

(c) Except as explicitly set forth in Section 10.4.1(a), Biogen Idec will have no further rights and Isis will have no further obligations with respect to the terminated ISIS-DMPK$_{Rx}$ R&D Plan.

(d) If (i) Biogen Idec terminates the Agreement under Section 10.2.1 (Biogen Idec's Termination for Convenience) or (ii) Isis terminates this Agreement under Section 10.2.4(b) (Isis' Right to Terminate) or Section 10.2.5 (Remedies for Failure to Use Commercially Reasonable Efforts), then the following additional terms will also apply:

(i) Biogen Idec will grant to Isis a sublicensable, worldwide, exclusive license or sublicense, as the case may be, to all Biogen Idec Technology Controlled by Biogen Idec as of the date of such reversion that Covers the Discontinued Product solely as necessary to Develop, make, have made, use, sell, offer for sale, have sold, import and otherwise Commercialize

the Discontinued Product in the Field (such license will be sublicensable by Isis in accordance with Section 4.1.2, *mutatis mutandis*);

(ii) Biogen Idec will assign back to Isis any Product-Specific Patent Rights that relate to the Discontinued Product previously assigned by Isis to Biogen Idec under this Agreement;

(iii) Biogen Idec will transfer to Isis for use with respect to the Development and Commercialization of the Discontinued Product, any Know-How data, results, regulatory information, filings, and files in the possession of Biogen Idec as of the date of such reversion that relate solely to such Discontinued Product, and any other information or material specified in Section 4.5;

(iv) Biogen Idec will license to Isis any trademarks that are specific to a Discontinued Product solely for use with such Discontinued Product, in accordance with Section 4.1.5, *mutatis mutandis*; *provided*, *however*, that in no event will Biogen Idec have any obligation to license to Isis any trademarks used by Biogen Idec both in connection with the Product and in connection with the sale of any other product or service, including any BIOGEN- or BIOGEN IDEC-formative marks;

(v) Isis will control and be responsible for all aspects of the Prosecution and Maintenance of all Jointly-Owned Program Patents, and Biogen Idec will provide Isis with (and will instruct its counsel to provide Isis with) all of the information and records in Biogen Idec's and its counsel's possession related to the Prosecution and Maintenance of such Jointly-Owned Program Patents; *provided*, *however*, if Isis intends to abandon any such Jointly-Owned Program Patents without first filing a continuation or substitution, then Isis will notify Biogen Idec of such intention at least 60 days before such Patent Right will become abandoned, and Biogen Idec will have the right, but not the obligation, to assume responsibility for the Prosecution and Maintenance thereof at its own expense with counsel of its own choice; and

(vi) Isis will have the obligation to pay royalties to Biogen Idec under Section 6.7 with respect to the Discontinued Product. Such payments will be governed by the financial provisions in Section 6.9, and the definition of Net Sales will apply to sales of Discontinued Product by Isis, in each case *mutatis mutandis*.

(e) If Isis terminates this Agreement due to Biogen Idec's material breach or Biogen Idec terminates this Agreement for convenience, upon Isis' written request pursuant to a mutually agreed supply agreement, Biogen will sell to Isis any bulk API and finished drug Product in Biogen Idec's possession at the time of such termination, at a price equal to [***].

(f) To the extent requested by Isis, Biogen Idec will promptly assign to Isis any Manufacturing Agreements identified by Isis to which Biogen Idec is a party.

10.4.4. Remedies Available to Biogen Idec for Isis' Material Breach After Option Exercise.

(a) **Termination of Committees and Information Sharing**. If, after Option exercise, Isis materially breaches this Agreement and fails to cure such breach within the time periods set forth under Section 10.2.4(a), and Biogen Idec does not wish to terminate this Agreement in its entirety (an "***Isis Breach Event***"), then, in addition to any other remedies Biogen Idec may have under this Agreement or otherwise, Biogen Idec will have the right to do any or all of the following in Biogen Idec's discretion:

(i) Terminate Isis' right to participate in the JSC, JPC and any other subcommittees or working groups established pursuant to this Agreement, each of which will be disbanded;

(ii) Terminate Isis' participation in any ongoing research and development programs under this Agreement and Biogen Idec's funding obligations associated therewith;

(iii) Solely make all decisions required or permitted to be made by such committees or the Parties collectively under this Agreement in connection with the Development and Commercialization of the Product; *provided*, *however*, that Biogen Idec will not have the right to create any obligations or incur any liabilities for or on behalf of Isis;

(iv) Exclude Isis from all discussions with Regulatory Authorities regarding Products, *except* to the extent Isis' participation is required by a Regulatory Authority or is otherwise reasonably necessary to comply with Applicable Law;

(v) Terminate Biogen Idec's obligation to make further disclosures of Know-How or other information to Isis pursuant to this Agreement, including pursuant to Section 4.5 and Section 5.2.2, other than reports required by Section 6.9.1, Section 10.4.3 (if applicable), and as reasonably required to permit Isis to perform its obligations under this Agreement; and

(vi) If Isis has not completed the Development activities that are its responsibility under the ISIS-DMPK$_{Rx}$ R&D Plan, then Biogen Idec may, but will not be obligated to, assume all responsibility for all such Development activities that would have otherwise been Isis' responsibility under this Agreement.

Isis will cooperate with the foregoing and provide to Biogen Idec and its Third Party contractors all Know-How, assistance, assignments and other support reasonably requested to assist Biogen Idec in assuming complete responsibility for the Development and Manufacture of the Products in an efficient and orderly manner.

(b) **Biogen Idec's Right of Setoff**. If there is [***] and Biogen Idec does not wish to [***], then, in addition to any other remedies Biogen Idec may have under this Agreement or otherwise, Biogen Idec may setoff against any amounts owed to Isis pursuant to ARTICLE 6 (Financial Provisions) [***] (the "***Setoff Amount***"). If Biogen Idec exercises its setoff right under this Section 10.4.4(b), Biogen Idec will provide Isis with a written certificate, signed by Biogen Idec's Chief Financial Officer, certifying that the amount setoff by Biogen Idec represents [***]. Notwithstanding the foregoing, if Isis notifies Biogen Idec in writing (a "***Setoff Dispute Notice***") that it disputes Biogen Idec's assertion that Isis is in material breach of this Agreement or the amount setoff by Biogen Idec (a "***Setoff Dispute***"), then (i) both Parties will participate in the dispute resolution process set forth on SCHEDULE 10.4.4(b), and (ii) pending the Parties' agreement regarding the appropriate setoff (if any) or a determination by the Advisory Panel of the proper amount that Biogen Idec may setoff (if any) in accordance with SCHEDULE 10.4.4(b), Biogen Idec will pay the Setoff Amount into an interest-bearing escrow account established for the purpose at a bank. If the Parties cannot settle their dispute by mutual agreement, then, in accordance with SCHEDULE 10.4.4(b) the Advisory Panel will determine (1) the amount (if any) that Biogen Idec may setoff against future payments to Isis going forward, and (2) whether any portion of the escrow account should be released to Isis or returned to Biogen Idec, *provided* that any decision or determination by the Advisory Panel (a "***Panel Decision***") will not be treated as an arbitral award but will be binding on the Parties until and unless a court of competent jurisdiction (the "***Trial Court***") has determined in a judgment regarding some or all

of the issues decided in the Panel Decision, and in any Action contemplated by the next sentence hereof the Trial Court will determine the facts and the law *de novo*, and will give a Panel Decision only such persuasive effect, if any, that after review of all of the facts and the law presented to the Trial Court by the Parties, the Trial Court deems appropriate, *provided*, that the Escrow Agent will comply with a Panel Decision that determines that any portion of the escrow account should be released to Isis or returned to Biogen Idec. If it is determined in a judgment by the Trial Court that Isis owes Biogen Idec any damages, then, during the pendency of any appeal of the Trial Court's decision (or, if the Trial Court's decision is not appealed, until Biogen Idec recoups such amount), Biogen Idec may setoff against any future payments to Isis under this Agreement the amount of any such damages not paid by Isis. If it is determined in a Trial Court that Biogen Idec has setoff an amount that exceeds the amount of losses, damages and expenses actually incurred by Biogen Idec as a result of Isis' breach of this Agreement, then Biogen Idec will promptly pay Isis the amount of such excess, plus interest on such amount as provided for in Section 6.12 (Interest on Late Payments), with interest accruing from the time Biogen Idec applied such excess setoff. If, with respect to a Setoff Dispute, Isis provides a Setoff Dispute Notice to Biogen Idec and Biogen Idec fails to do any of the following: (X) appoint a member of the Advisory Panel to the extent required in Section 2 of SCHEDULE 10.4.4(b); (Y) meet with the Advisory Panel as required in Section 3 of SCHEDULE 10.4.4(b); or (Z) pay the Setoff Amount into an interest-bearing escrow account established for the purpose at a bank, then Biogen Idec will forfeit its right to set off under this Section 10.4.4(b) and SCHEDULE 10.4.4(b) with respect to any and all Setoff Disputes.

ARTICLE 11.
CONFIDENTIALITY

11.1. **Confidentiality; Exceptions**. Except to the extent expressly authorized by this Agreement or otherwise agreed in writing, the Parties agree that, during the Agreement Term and for five years thereafter, the receiving Party (the "***Receiving Party***") and its Affiliates will keep confidential and will not publish or otherwise disclose or use for any purpose other than as provided for in this Agreement any confidential or proprietary information or materials, patentable or otherwise, in any form (written, oral, photographic, electronic, magnetic, or otherwise) which is disclosed to it by the other Party (the "***Disclosing Party***") or its Affiliates or otherwise received or accessed by a Receiving Party in the course of performing its obligations or exercising its rights under this Agreement, including trade secrets, Know-How, inventions or discoveries, proprietary information, formulae, processes, techniques and information relating to the past, present and future marketing, financial, and research and development activities of any product or potential product or useful technology of the Disclosing Party or its Affiliates and the pricing thereof (collectively, "***Confidential Information***").

11.2. **Prior Confidentiality Agreement Superseded**. As of the Effective Date, this Agreement supersedes the Confidential Disclosure Agreement executed by Isis and Biogen Idec on February 28, 2011 (including any and all amendments thereto). All information exchanged between the Parties under such Confidential Disclosure Agreement will be deemed Confidential Information hereunder and will be subject to the terms of this ARTICLE 11.

11.3. **Authorized Disclosure**. Except as expressly provided otherwise in this Agreement, a Receiving Party or its Affiliates may use and disclose to Third Parties Confidential Information of the Disclosing Party as follows: (i) solely in connection with the performance of its obligations or exercise of rights granted or reserved in this Agreement under confidentiality provisions no less restrictive than those in this Agreement, *provided*, that Confidential Information may be disclosed by a Receiving Party to a governmental entity or agency without requiring such entity or agency to enter into a confidentiality agreement; (ii) to the extent reasonably necessary to file or prosecute patent, copyright and trademark applications (subject to Section 11.4 below), complying with applicable governmental regulations, obtaining Approvals, conducting Pre-Clinical Studies or Clinical Studies, marketing the Product, or as otherwise required by applicable law, regulation, rule or legal process (including the rules of the SEC and any stock exchange); *provided, however*, that if a Receiving Party or any of its Affiliates is required by law or regulation to make any such disclosure of a Disclosing Party's Confidential Information it will, except where impracticable for necessary disclosures, give reasonable advance notice to the Disclosing Party of such disclosure requirement and will use its reasonable efforts to secure confidential treatment of such Confidential Information required to be disclosed; (iii) in communication with actual or potential lenders, investors, merger partners, acquirers, consultants, or professional advisors on a need-to-know basis, in each case under confidentiality provisions no less restrictive than those of this Agreement; (iv) to the extent such disclosure is required to comply with existing expressly stated contractual obligations owed to such Party's or its Affiliates' licensor with respect to any intellectual property licensed to the other Party under this Agreement; or (v) as mutually agreed to in writing by the Parties.

11.4. **Press Release; Publications; Disclosure of Agreement**.

11.4.1. **Public Announcements**. On or promptly after the Effective Date, the Parties will jointly issue a public announcement of the execution of this Agreement in form and substance mutually agreed by the Parties. Except to the extent required to comply with applicable law, regulation, rule or legal process or as otherwise permitted in accordance with this Section 11.4, neither Party nor such Party's Affiliates will make any public announcements, press releases or other public disclosures concerning this Agreement or the terms or the subject matter hereof without the prior written consent of the other, which will not be unreasonably withheld, conditioned or delayed.

11.4.2. **Use of Name**. Except as set forth in Section 11.4.9, neither Party will use the other Party's name in a press release or other publication without first obtaining the prior consent of the Party to be named.

11.4.3. **Notice of Significant Events**. Each party will immediately notify (and provide as much advance notice as possible, but at a minimum two Business Days advance notice to) the other Party of any event materially related to the Product (including in such notice any disclosure of starting/stopping of a Clinical Study, clinical data or results, material regulatory discussions, filings, Approval or Biogen Idec's sales projections) so the Parties may analyze the need for or desirability of publicly disclosing or reporting such event.

11.4.4. **Prior to Option Exercise**. Prior to Option exercise, the Product is the sole property of Isis, and Isis will have the sole right, consistent with its practice with its other compounds and products, to issue press releases, publish, present or otherwise disclose the progress and results regarding the Product to the public; *provided*, that with respect to any proposed press release or other similar public communication by Isis disclosing regulatory discussions, the efficacy or safety data or clinical results related to the Product, (i) Isis will submit such proposed communication to Biogen Idec for review at least two Business Days in advance of such proposed public disclosure, (ii) Biogen Idec will have the right to review and recommend changes to such communication, and (iii) Isis will in good faith consider any changes that are timely recommended by Biogen Idec.

11.4.5. **After Option Exercise**. After Option exercise, Biogen Idec will have the sole right, consistent with its practice with its other compounds and products, to issue press releases, publish, present or otherwise disclose the progress and results regarding the Product to the public; *provided*, that with respect to any proposed press release or other similar public communication by Biogen Idec disclosing regulatory discussions, the efficacy or safety data or results related to the Product or Biogen Idec's sales projections, (i) Biogen Idec will submit such proposed communication to Isis for review at least two Business Days in advance of such proposed public disclosure, (ii) Isis will have the right to review and recommend changes to such communication, and (iii) Biogen Idec will in good faith consider any changes that are timely recommended by Isis.

11.4.6. **Scientific or Clinical Presentations**. Regarding any proposed scientific publications or public presentations related to summaries of results from any Clinical Studies generated by Isis or Biogen Idec for the Product, the Parties acknowledge that scientific lead time is a key element of the value of the Product under this Agreement and further agree to use Commercially Reasonable Efforts to control public scientific disclosures of the results of the Development activities under this Agreement to prevent any potential adverse effect of any premature public disclosure of such results. The Parties will establish a procedure for publication review and each Party will first submit to the other Party through the Joint Patent Committee an early draft of all such publications or presentations, whether they are to be presented orally or in written form, at least 45 days prior to

submission for publication including to facilitate the publication of any summaries of Clinical Studies data and results as required on the clinical trial registry of each respective Party. Each Party will review such proposed publication in order to avoid the unauthorized disclosure of a Party's Confidential Information and to preserve the patentability of inventions arising from the ISIS-DMPK$_{Rx}$ R&D Plan. If, during such 45 day period, the other Party informs such Party that its proposed publication contains Confidential Information of the other Party, then such Party will delete such Confidential Information from its proposed publication. In addition, if at any time during such 45 day period, the other Party informs such Party that its proposed publication discloses inventions made by either Party in the course of the Development under this Agreement that have not yet been protected through the filing of a patent application, or the public disclosure of such proposed publication could be expected to have a material adverse effect on any Patent Rights or Know-How solely owned or Controlled by such other Party, then such Party will either (i) delay such proposed publication for up to 60 days from the date the other Party informed such Party of its objection to the proposed publication, to permit the timely preparation and first filing of patent application(s) on the information involved or (ii) remove the identified disclosures prior to publication.

11.4.7 **SEC Filings**. Each Party will give the other Party a reasonable opportunity to review all material filings with the SEC describing the terms of this Agreement prior to submission of such filings, and will give due consideration to any reasonable comments by the non-filing Party relating to such filing.

11.4.8 **Subsequent Disclosure**. Notwithstanding the foregoing, to the extent information regarding this Agreement or the Product has already been publicly disclosed, either Party (or its Affiliates) may subsequently disclose the same information to the public without the consent of the other Party.

11.4.9 **Acknowledgment**. Each Party will acknowledge in any press release, public presentation or publication regarding the collaboration or the Product, the other Party's role in discovering and developing the Product or Discontinued Product, as applicable, that the Product is under license from Isis and otherwise acknowledge the contributions from the other Party, and each Party's stock ticker symbol (e.g., Nasdaq: ISIS, BIIB). Isis may include the Product (and identify Biogen Idec as its partner for the Product) in Isis' drug pipeline.

ARTICLE 12.
MISCELLANEOUS

12.1. Dispute Resolution.

12.1.1. Escalation. In the event of any Dispute (other than a Setoff Dispute, which Setoff Dispute will be resolved pursuant to Section 12.1.3, or dispute regarding the construction, validity or enforcement of either Party's Patents, which disputes will be resolved pursuant to Section 12.2), either Party may, within 30 days after either Party notifies the other Party that the Dispute has not been resolved (*provided, that* such notice cannot be given less than 30 days after the Dispute has arisen), make a written request that the Dispute be referred for resolution to the Executive Vice President, Business Development of Biogen Idec and the Chief Operating Officer of Isis (the "***Executives***"). Within 60 days of either Party's written request that the Dispute be referred to the Executives, the Executives will meet in person at a mutually acceptable time and location or by means of telephone or video conference to negotiate a settlement of a Dispute. Each Party may elect to have such Party's JSC representatives participate in such meeting, if desired, provided that it provides the other Party with reasonable advance notice of such intent so as to enable the other Party to have its JSC representatives also participate in such meeting, if desired. If the Executives fail to resolve the Dispute within such 60 day period, then the Dispute will be referred to mediation under Section 12.1.2.

12.1.2. Mediation. If a Dispute subject to Section 12.1.1 cannot be resolved pursuant to Section 12.1.1, or if neither Party timely makes the written request that the Dispute be referred to the Executives, the Parties will resolve any such Dispute in accordance with the dispute resolution procedures set forth in SCHEDULE 12.1.2.

12.1.3. Setoff Disputes. Setoff Disputes will be resolved in accordance with Section 10.4.4(b) and SCHEDULE 10.4.4(b).

12.2. Governing Law; Jurisdiction; Venue; Service of Process.

12.2.1. This Agreement and any Dispute will be governed by and construed and enforced in accordance with the laws of the State of Delaware, U.S.A., without reference to conflicts of laws principles.

12.2.2. Subject to the provisions of Section 12.1, each Party by its execution hereof, (a) hereby irrevocably submits to the exclusive jurisdiction of the United States District Court for the District of Delaware (or, if but only if such court lacks, or will not exercise, subject matter jurisdiction over the entirety of a Dispute, the Court of Chancery of the State of Delaware, or, if but only if such court lacks, or will not exercise, subject matter jurisdiction over the entirety of a Dispute, the Superior Court of the State of Delaware, with respect to the Dispute) for the purpose of any Dispute arising between the Parties in connection with this Agreement (each, an "***Action***") and (b) hereby waives to the extent not prohibited by Applicable Law, and agrees not to assert, by way of motion, as a defense or otherwise, in any such Action, any claim that it is not subject personally to the jurisdiction of the above-named courts, that venue in the above-named courts is improper, that its property is exempt or immune from attachment or execution, that any such Action brought in the above-named courts should be dismissed on grounds of forum non conveniens, should be transferred or removed to any court other than the above-named courts, or should be stayed by reason of the pendency of some other proceeding in any other court other than the above-named courts, or that this Agreement or the subject matter hereof may not be enforced in or by

such courts and (c) hereby agrees not to commence any such Action other than before the above-named courts. Notwithstanding the previous sentence, a Party may commence any Action in a court other than the above-named court solely for the purpose of enforcing an order or judgment issued by the above-named court.

12.2.3. Each Party hereby agrees that service of process: (a) made in any manner permitted by Delaware law, or (b) made by overnight express courier service (signature required), prepaid, at its address specified pursuant to Section 12.7, will constitute good and valid service of process in any such Action and (c) waives and agrees not to assert (by way of motion, as a defense, or otherwise) in any such Action any claim that service of process made in accordance with clause (a) or (b) does not constitute good and valid service of process.

12.3. Remedies. Notwithstanding anything to the contrary in this Agreement, each Party will be entitled to seek, in addition to any other right or remedy it may have, at law or in equity, a temporary restraining order or a preliminary injunction, without the posting of any bond or other security, enjoining or restraining the other Party from any violation or threatened violation of this Agreement, and the Parties agree that in the event of a threatened or actual material breach of this Agreement injunctive relief would be appropriate. Neither Party will be entitled to recover any Losses relating to any matter arising under one provision of this Agreement to the extent that such Party has already recovered Losses with respect to such matter pursuant to other provisions of this Agreement (including recoveries under Section 9.1 or Section 9.2, and the offsets under Section 6.8.3(c)). Except for the offsets and credits explicitly set forth in Section 6.10, Section 6.8.3(b), Section 6.8.3(d) and Section 10.4.4(b), neither Party will have the right to setoff any amount it is owed or believes it is owed against payments due or payable to the other Party under this Agreement.

12.4. Assignment and Successors. Neither this Agreement nor any obligation of a Party hereunder may be assigned by either Party without the consent of the other, which will not be unreasonably withheld, delayed or conditioned, except that each Party may assign this Agreement and the rights, obligations and interests of such Party, in whole or in part, without the other Party's consent, to any of its Affiliates, to any purchaser of all or substantially all of its assets or all or substantially all of its assets to which this Agreement relates or to any successor corporation resulting from any merger, consolidation, share exchange or other similar transaction; *provided*, if Biogen Idec transfers or assigns this Agreement to [***] described in this Agreement, then Biogen Idec (or such Affiliate), will [***] due Isis under ARTICLE 6 for the [***] such that Isis receives [***] assignment. In addition, Isis may assign or transfer its rights to receive payments under this Agreement (but no liabilities), without Biogen Idec's consent, to an Affiliate or to a Third Party in connection with a payment factoring transaction. Any purported assignment or transfer made in contravention of this Section 12.4 will be null and void.

The [***].

To the extent Isis utilizes a [***] in any year, Isis will [***] to Biogen Idec [***]. To assist Biogen Idec in determining when [***] pursuant to the foregoing sentence, beginning with the first Annual tax return for the year in which Biogen Idec [***] payment under this Section 12.4, and each year thereafter (including, for clarity, all years in which Isis utilizes a [***]), Isis will provide Biogen Idec with Isis' Annual tax returns (federal and state) and, in years in which Isis utilizes [***], supporting documentation for such [***]. Notwithstanding the foregoing, if the [***].

12.5. **Change of Control**. If, at any time during the Option Period, a Change of Control occurs involving Isis and a Person that, at the time of the consummation of such Change of Control, is developing in human clinical trials or commercializing a Directly Competitive Product within the Field or, at any time after such consummation of the Change of Control, develops or acquires a Directly Competitive Product (such Person being hereinafter referred to as a "***Competing Acquirer***") and such Competing Acquirer has not, within [***] of either consummation of the Change of Control in the event the Directly Competitive Product is being developed in human clinical trials or commercialized as of such consummation date or otherwise within [***] of the date of first development or acquisition of such Directly Competitive Product (the "***Divestiture Period***") divested itself of the Directly Competitive Product, terminated development and commercialization of such Directly Competitive Product or assigned this Agreement pursuant to Section 12.3 to a Third Party that is not itself developing or commercializing a Directly Competitive Product, then (i) Isis will provide written notice to Biogen Idec of the closing of such Change of Control or Divestiture Period, as applicable, (ii) [***] and (iii) and Biogen Idec will have the right, within [***] following such written notice, to either:

(a) if unexercised, exercise the Option by notifying Isis in writing of Biogen Idec's election to license the Product at a prorated license fee payment as compared to the license fee payment set forth in Section 6.3, based upon the stage of Development of the Product at the time of Change of Control or Divestiture Period, as applicable, which license fee payments are set forth on SCHEDULE 12.5 hereto. If Biogen Idec exercises the Option pursuant to this Section 12.5, Biogen Idec will not be obligated [***]. Upon Biogen Idec's exercise of its Option pursuant to this Section 12.5(a), Biogen Idec will be deemed to have obtained and Isis will be deemed to have granted the license set forth in Section 4.1.1; or

(b) Allow such [***] period to lapse without providing any such notice of election under this Section 12.5, or otherwise provide Isis with written notice within such period electing not to exercise its Option pursuant to Section 12.5(a) above, in either of which cases Isis and Biogen Idec will continue to exercise their rights and perform their respective obligations with respect to the Product under the terms of this Agreement.

Upon Biogen Idec's exercise of its Option pursuant to Section 12.5(a) above, Isis will carry out its technology transfer obligations pursuant to Section 4.2 with respect to the Product. For the avoidance of doubt, except as set forth in this Section 12.5, all other terms and conditions of this Agreement will apply to any such license granted pursuant to Biogen Idec's exercise of its rights hereunder.

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

12.7. **Notices**. Any notice or request required or permitted to be given under or in connection with this Agreement will be deemed to have been sufficiently given if in writing and personally delivered or sent by certified mail (return receipt requested), facsimile transmission (receipt verified), or overnight express courier service (signature required), prepaid, to the Party for which such notice is intended, at the address set forth for such Party below:

If to Isis, addressed to:	Isis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, CA 92010 Attention: Chief Operating Officer Fax: 760-918-3592
with a copy to:	Isis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, CA 92010 Attention: General Counsel Fax: 760-268-4922
If to Biogen Idec, addressed to:	Biogen Idec MA Inc. 14 Cambridge Center Cambridge, MA 02142 Attention: Richard Brudnick Fax: 617-679-2617

with a copy to: Ropes & Gray LLP
Prudential Tower
800 Boylston Street
Boston, MA 02199-3600
Attention: Marc A. Rubenstein, Esq.
Fax: 617-235-0706

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

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

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

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

12.11. **Entire Agreement**. This Agreement, together with the Schedules and Appendices hereto, sets forth all the covenants, promises, agreements, warranties, representations, conditions and understandings between the Parties and supersedes and terminates all prior agreements and understanding between the Parties. There are no covenants, promises, agreements, warranties, representations, conditions or understandings, either oral or written, between the Parties other than as set forth herein and therein. No subsequent alteration, amendment, change or addition to this Agreement will be binding upon the Parties hereto unless reduced to writing and signed by the respective authorized officers of the Parties.

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

12.13. **Interpretation**. Except as otherwise explicitly specified to the contrary, (a) references to a section, exhibit or schedule means a section of, or schedule or exhibit to this Agreement, unless another agreement is specified, (b) the word “including” (in its various forms) means “including without limitation,” (c) the words “shall” and “will” have the same meaning, (d) references to a particular statute or regulation include all rules and regulations thereunder and any predecessor or successor statute, rules or regulation, in each case as amended or otherwise modified from time to time, (e) words in the singular or plural form include the plural and singular form, respectively, (f) references to a particular Person include such Person’s successors and assigns to the extent not prohibited by this Agreement, (g) unless otherwise specified, “$” is in reference to United States dollars, and (h) the headings contained in this Agreement, in any exhibit or schedule to this Agreement and in the table of contents to this Agreement are for convenience only and will not in any way affect the construction of or be taken into consideration in interpreting this Agreement.

12.14. **Books and Records**. Any books and records to be maintained under this Agreement by a Party or its Affiliates or Sublicensees will be maintained in accordance with U.S. Generally Accepted Accounting Principles (or any successor standard), consistently applied.

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

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

12.17. **Supremacy**. In the event of any express conflict or inconsistency between this Agreement and any Schedule or Appendix hereto, the terms of this Agreement will apply. The Parties understand and agree that the Schedules and Appendices hereto are not intended to be the final and complete embodiment of any terms or provisions of this Agreement, and are to be updated from time to time during the Agreement Term, as appropriate and in accordance with the provisions of this Agreement.

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

12.19. **Compliance with Laws**. Each Party will, and will ensure that its Affiliates and Sublicensees will, comply with all relevant laws and regulations in exercising its rights and fulfilling its obligations under this Agreement.

[SIGNATURE PAGE FOLLOWS]

* - * - * - *

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

BIOGEN IDEC MA INC.

By: /s/ Doug Williams
Name: Doug Williams
Title: Executive Vice President, Research and Development

SIGNATURE PAGE TO DMPK RESEARCH, DEVELOPMENT, OPTION AND LICENSE AGREEMENT

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

ISIS PHARMACEUTICALS, INC.

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

SIGNATURE PAGE TO DMPK RESEARCH, DEVELOPMENT, OPTION AND LICENSE AGREEMENT

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APPENDIX 1

DEFINITIONS

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

"***Acceptance***" means, with respect to an NDA, MAA or JNDA filed for a Product, (a) in the United States, the receipt of written notice from the FDA in accordance with 21 C.F.R. §314.101(a)(2) that such NDA is officially "*filed*," (b) in the European Union, receipt by Biogen Idec of written notice of acceptance by the EMA of such MAA for filing under the centralized European procedure in accordance with any feedback received from European Regulatory Authorities; *provided that* if the centralized filing procedure is not used, then Acceptance will be determined upon the acceptance of such MAA by the applicable Regulatory Authority in a Major Country in the EU, and (c) in Japan, receipt by Biogen Idec of written notice of acceptance of filing of such JNDA from the Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto).

"***Action***" has the meaning set forth in Section 12.2.2.

"***Additional Core IP***" means Third Party intellectual property that is necessary to [***]. For clarity, Additional Core IP does not include any Patent Rights claiming (or intellectual property related to) [***].

"***Additional R&D Plan Costs***" means [***].

"***Advisory Panel***" has the meaning in SCHEDULE 10.4.4(b) of this Agreement.

"***Affiliate***" of an entity means any corporation, firm, partnership or other entity which directly or indirectly through one or more intermediaries controls, is controlled by or is under common control with a Party to this Agreement. An entity will be deemed to control another entity if it (i) owns, directly or indirectly, at least 50% of the outstanding voting securities or capital stock (or such lesser percentage which is the maximum allowed to be owned by a foreign corporation in a particular jurisdiction) of such other entity, or has other comparable ownership interest with respect to any entity other than a corporation; or (ii) has the power, whether pursuant to contract, ownership of securities or otherwise, to direct the management and policies of the entity. For clarity, Regulus Therapeutics Inc. will not be deemed an "*Affiliate*" of Isis for the purposes of this Agreement under any circumstances.

"***Agreement***" has the meaning set forth in the Preamble of this Agreement.

"***Agreement Term***" has the meaning set forth in Section 10.1.

"***Alliance Manager***" has the meaning set forth in Section 1.2.6.

"***ANDA***" means an Abbreviated New Drug Application and all amendments and supplements thereto filed with the FDA, or the equivalent application filed with any equivalent agency or governmental authority outside the U.S. (including any supra-national agency such as the EMA in the EU).

"***Annual***" means the period covering a Calendar Year or occurring once per Calendar Year, as the context requires.

"***API***" means the bulk active pharmaceutical ingredient manufactured in accordance with cGMP for the Product.

"***Applicable Law***" or "***Law***" means all applicable laws, statutes, rules, regulations and other pronouncements having the effect of law of any federal, national, multinational, state, provincial, county, city or other political subdivision, agency or other body, domestic or foreign, including any applicable rules, regulations, guidelines, or other requirements of the Regulatory Authorities that may be in effect from time to time.

"***Approval***" means, with respect to the Product in any regulatory jurisdiction, approval from the applicable Regulatory Authority sufficient for the manufacture, distribution, use, marketing and sale of the Product in such jurisdiction in accordance with Applicable Laws. In jurisdictions where the applicable Regulatory Authority sets the pricing or reimbursement authorizations necessary for the general marketing and sale of the Product in the marketplace, Approval will not be deemed to have occurred if the final approval to market and sell the Product is being withheld because Biogen Idec (or its Affiliate or Sublicensee) and the Regulatory Authority have not yet determined pricing or reimbursement even if all other approvals, licenses, registrations or authorizations necessary for marketing, sale or use of the Product in such jurisdiction have been obtained. "Approval" does not include authorization by a Regulatory Authority to conduct named patient, compassionate use or other similar activities.

"***ASO***" means a single-stranded oligonucleotide compound, or analog, variant, mimic, or mimetic thereof, having a sequence that is at least six bases long and that modulates expression or splicing of a gene target via the binding, partially or wholly, of such compound to the RNA of such gene target.

"***Audit Report***" has the meaning set forth in Section 6.10.

"***Bankruptcy Code***" has the meaning set forth in Section 10.2.7(b).

"***Biogen Idec***" has the meaning set forth in the Preamble of this Agreement.

"***Biogen Idec's FTE Cost***" means the FTE Rate applicable to Biogen Idec, *multiplied* by the applicable number of FTEs.

"***Biogen Idec Full Royalty***" has the meaning set forth in Section 6.6.1.

"***Biogen Idec Know-How***" means any Know-How owned, used, developed by, or licensed to Biogen Idec or its Affiliates, in each case to the extent Controlled by Biogen Idec or its Affiliates on the Effective Date or at any time during the Agreement Term, *but specifically excluding* the Biogen Idec Program Know-How.

"***Biogen Idec Patents***" means any Patent Rights included in the Biogen Idec Technology.

"***Biogen Idec Product-Specific Patents***" means all Product-Specific Patents owned, used, developed by, or licensed to Biogen Idec or its Affiliates, in each case to the extent Controlled by Biogen Idec or its Affiliates on the Effective Date or at any time during the Agreement Term.

"***Biogen Idec Program Know-How***" has the meaning set forth in Section 7.1.2.

"***Biogen Idec Program Patents***" has the meaning set forth in Section 7.1.2.

"***Biogen Idec Program Technology***" has the meaning set forth in Section 7.1.2.

"***Biogen Idec-Prosecuted Patents***" has the meaning set forth in Section 7.2.4.

"***Biogen Idec Reduced Royalty***" has the meaning set forth in Section 6.6.2(c).

"***Biogen Idec Supported Pass-Through Costs***" means [***].

"***Biogen Idec Technology***" means the Biogen Idec Program Technology, Jointly-Owned Program Technology, Biogen Idec Product-Specific Patents and any trademarks described in Section 4.1.5, owned, used, developed by, or licensed to Biogen Idec or its Affiliates that is necessary or useful to Develop, register, Manufacture or Commercialize the Product.

"***Biogen-Initiated Changes***" means any changes (including number of subjects, duration of dosing, additional studies, additional endpoints, additional analysis, etc.) to the ISIS-DMPK$_{Rx}$ R&D Plan that are requested by Biogen Idec (including any changes required by a Regulatory Authority).

"***Breaching Party***" means the Party that is believed by the Non-Breaching Party to be in material breach of this Agreement.

"***Business Day***" means any day other than a Saturday or Sunday on which banking institutions in New York, New York are open for business.

"***Calendar Quarter***" means a period of three consecutive months ending on the last day of March, June, September, or December, respectively, and will also include the period beginning on the Effective Date and ending on the last day of the Calendar Quarter in which the Effective Date falls.

"***Calendar Year***" means a year beginning on January 1 (or, with respect to 2012, the Effective Date) and ending on December 31.

"***cGMP***" means current Good Manufacturing Practices as specified in the United States Code of Federal Regulations, ICH Guideline Q7A, or equivalent laws, rules, or regulations of an applicable Regulatory Authority at the time of manufacture.

"***Change of Control***" means, with respect to a Party, (a) a merger or consolidation of such Party with a Third Party which results in the voting securities of such Party outstanding immediately prior thereto ceasing to represent at least 50% of the combined voting power of the surviving entity immediately after such merger or consolidation, (b) a transaction or series of related transactions in which a Third Party, together with its Affiliates, becomes the owner of 50% or more of the combined voting power of the outstanding securities of such Party, (c) the sale or other transfer to a Third Party of all or substantially all of such Party's business to which the subject matter of this Agreement relates, or (d) the stockholders or equity holders of such Party will approve a plan of complete liquidation of such Party or an agreement for the sale or disposition by such Party of all or a substantial portion of such Party's assets, other than pursuant to the transaction as described above or to an Affiliate. Notwithstanding the foregoing, the sale or issuance of shares in exchange for cash for purposes of a *bona fide* financing will not constitute a Change of Control.

"***Claims***" has the meaning set forth in Section 9.1.

"***Clinical Study***" or "***Clinical Studies***" means a Phase 1 Trial, Phase 2 Trial, Phase 3 Trial or Phase 4 Trial, or such other study in humans that is conducted in accordance with good clinical practices and is designed to generate data in support or maintenance of an NDA, MAA or other similar marketing application.

"***Clinical Supplies***" means API and finished drug Product for use in a Clinical Study.

"***CMO***" means a Third Party contract manufacturer Manufacturing API or finished drug Product for any purpose under this Agreement.

"***Collaborator IP***" has the meaning set forth in Section 7.1.3(b).

"***Commercial Supplies***" has the meaning set forth in Section 1.5.2.

"***Commercialize***," "***Commercialization***" or "***Commercializing***" means any and all activities directed to marketing, promoting, detailing, distributing, importing, having imported, exporting, having exported, selling or offering to sell the Product following receipt of Approval for the Product in the applicable country, including conducting pre-and post-Approval activities, including studies reasonably required to increase the market potential of the Product and studies to provide improved formulation and Product delivery, and launching and promoting the Product in each country.

"***Commercializing Party***" means (a) Biogen Idec, with respect to the Product that is being Developed and Commercialized by or on behalf of Biogen Idec, its Affiliates or Sublicensees hereunder, and (b) Isis, with respect to a Discontinued Product that is being Developed and Commercialized by or on behalf of Isis, its Affiliates or Sublicensees hereunder.

"***Commercially Reasonable Efforts***" means the carrying out of discovery, research, development or commercialization activities using good-faith commercially reasonable and diligent efforts that the applicable Party would reasonably devote to a compound or product of similar market potential or profit potential at a similar stage in development or product life resulting from its own research efforts, based on conditions then prevailing and taking into account, without limitation, issues of safety and efficacy, regulatory authority-approved labeling, product profile, the competitiveness of alternative products in the marketplace, the likely timing of the product's entry into the market, the patent and other proprietary position, the likelihood of Approval and other relevant scientific, technical and commercial factors. Without limiting any of the foregoing, Commercially Reasonable Efforts as it applies to Biogen Idec's Development or Commercialization of the Product hereunder includes the use of Commercially Reasonable Efforts to perform the "*General Activities*" described in SCHEDULE 5.1.1, and Commercially Reasonable Efforts as it applies to Isis' Development of the Product hereunder includes use of Commercially Reasonable Efforts to adhere to the activities and timelines set forth in the ISIS-DMPK$_{Rx}$ R&D Plan.

"***Competing Acquirer***" has the meaning set forth in Section 12.5.

"***Competitive Infringement***" has the meaning set forth in Section 7.5.1.

"***Compound***" means any ASO that is designed to bind to the RNA that encodes DMPK, where such ASO is discovered by Isis prior to or in the performance of the ISIS-DMPK$_{Rx}$ R&D Plan, including the Development Candidate.

"***Confidential Information***" has the meaning set forth in Section 11.1. "*Confidential Information*" does not include information that:

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

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

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

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

"***Conflicting Patent Right***" has the meaning set forth in Section 7.2.4(c).

"***Control***" or "***Controlled***" means possession of the ability to grant a license or sublicense hereunder without violating the terms of any agreement with any Third Party; *provided*, *however*, that if a Party has a right to grant a license or sublicense, with respect to an item of intellectual property to the other Party only upon payment of compensation (including milestones or royalties) to a Third Party ("***Third Party Compensation***") (other than Isis Supported Pass-Through Costs in the case of Isis, and other than Biogen Idec Supported Pass-Through Costs in the case of Biogen Idec), then the first Party will be deemed to have "*Control*" of the relevant item of intellectual property only if the other Party agrees to bear the cost of such Third Party Compensation. Notwithstanding anything to the contrary under this Agreement, with respect to any Third Party that becomes an Affiliate of a Party after the Effective Date (including a Third Party acquirer), no intellectual property of such Third Party will be included in the licenses granted hereunder by virtue of such Third Party becoming an Affiliate of such Party.

"***Cover***," "***Covered***" or "***Covering***" means, with respect to a patent, that, but for rights granted to a Person under such patent, the act of making, using or selling by such Person would infringe a Valid Claim included in such patent, or in the case of a patent that is a patent application, would infringe a Valid Claim in such patent application if it were to issue as a patent.

"***CREATE Act***" means the Cooperative Research and Technology Enhancement Act of 2004, 35 U.S.C. § 103(c)(2)-(c)(3).

"***CTD***" has the meaning set forth in Section 4.3.

"***Deficiency Notice***" has the meaning set forth in Section 3.1.2.

"***Develop***," "***Developing***" or "***Development***" means with respect to the Product, any and all discovery, characterization, or preclinical (including IND-Enabling Toxicology Studies), clinical, or regulatory activity with respect to the Product to seek Approval (including the submission of all necessary filings with applicable Regulatory Authorities to support such preclinical and clinical activities and Approval), including human clinical trials conducted after Approval of the Product to seek Approval for additional indications for the Product.

"Development Candidate" means a Compound that is reasonably determined by Isis' RMC in accordance with Isis' standard procedures for designating development candidates [***] as ready to start IND-Enabling Toxicology Studies. The checklist Isis uses as of the Effective Date when reviewing potential development candidates for approval is attached hereto as APPENDIX 3.

"***Development Candidate Data Package***" means, with respect to a [***], the [***]; *provided* such package contains the [***]. The checklist Isis uses as of the Effective Date when reviewing potential development candidates for approval is attached hereto as APPENDIX 3.

"***Diagnostic Option***" has the meaning set forth in Section 3.2.1.

"***Directly Competitive Product***" means any product, other than the Product, that is designed to bind to the RNA that encodes DMPK.

"***Disclosing Party***" has the meaning set forth in Section 11.1.

"***Discontinued Product***" means the Product upon termination of this Agreement.

"***Dispute***" means any dispute arising between the Parties relating to, arising out of or in any way connected with this Agreement or any term or condition hereof, or the performance by either Party of its obligations hereunder, whether before or after termination of this Agreement that cannot be resolved by the Parties.

"***Divestiture Period***" has the meaning set forth in Section 12.5.

"***DMPK***" means the gene, dystrophia myotonica protein kinase (GenBank accession # NM_001081560.1; Gene ID: 1760), or any alternative splice variants, mutants, polymorphisms and fragments thereof.

"***DOJ***" has the meaning set forth in Section 3.1.4(a).

"***Effective Date***" has the meaning set forth in the Preamble of this Agreement.

"***EMA***" means the European Medicines Agency and any successor entity thereto.

"***Estimated Lock Date***" has the meaning set forth in Section 3.1.1.

"***European Union***" or "***EU***" means each and every country or territory that is officially part of the European Union.

"***Excluded Payments***" means (i) royalty or profit sharing payments, or any other type of payment based on periodic sales of a Product; (ii) payments made in consideration of Isis' or Isis' Affiliate's equity or debt securities at fair market value; (iii) payments made to pay for or reimburse Isis or Isis' Affiliate for the fully-burdened cost of research and development; (iv) payments made to pay for or reimburse Isis or Isis' Affiliate for the cost of prosecuting, maintaining or defending Patent Rights; and (v) payments made to Isis or Isis' Affiliate to pass-through to a Third Party in satisfaction of a payment obligation Isis or Isis' Affiliate has to such Third Party.

"***Executives***" has the meaning set forth in Section 12.1.1.

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

"***Field***" means the prophylactic or therapeutic use or form of administration of the Product for any indication.

"***First Commercial Sale***" means the first sale of the Product by Biogen Idec, its Affiliate or its Sublicensee to a Third Party in a particular country after Approval of the Product has been obtained in such country.

"***Follow-On Agreement***" has the meaning set forth in Section 2.1.2.

"***Follow-On Compound***" means any ASO that is designed to bind to the RNA that encodes DMPK discovered by or on behalf of Isis following exercise of the Option by Biogen Idec.

"***Follow-On Interest Notice***" has the meaning set forth in Section 2.1.2(a).

"***Follow-On Negotiation Notice***" has the meaning set forth in Section 2.1.2.

"***FTC***" has the meaning set forth in Section 3.1.4(a).

"***FTE***" means a total of 47 weeks or 1880 hours per year of work on the Development, Manufacturing or Commercialization of a Product carried out by employees of a Party having the appropriate relevant expertise to conduct such activities.

"***FTE Rate***" means $[***] for the Calendar Year 2012. The FTE Rate will be increased each Calendar Year thereafter by the [***].

"***Full Royalty Period***" has the meaning set forth in Section 6.6.2(a).

"***Fully Absorbed Cost of Goods***" means the costs incurred by Isis as determined using the methodology set forth in SCHEDULE 4.5.3 fairly applied and as employed on a consistent basis throughout Isis' operations.

"***Generic Product***" means one or more Third Party product(s) (i) having the same active pharmaceutical ingredient as the Product and for which in the U.S. an ANDA has been filed naming the Product as the reference listed drug or outside of the U.S., an equivalent process where bioequivalence to the Product has been asserted, and (ii) such Third Party product(s) when taken in the aggregate have a market share (measured in number of prescriptions with the numerator of such fractional share being such Third Party product(s) taken in the aggregate, and the denominator being the total of such Third Party product(s) taken in the aggregate plus the Product taken in the aggregate, as provided by IMS) during the applicable Calendar Quarter in such country of at least [***]%.

"***GLP***" means the then-current good laboratory practice standards promulgated or endorsed by the FDA as defined in 21 C.F.R. Part 58, and comparable foreign regulatory standards.

"***HSR Act***" means the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, and the rules and regulations promulgated thereunder.

"***HSR Clearance***" means all applicable waiting periods under the HSR Act with respect to the transactions contemplated under this Agreement have expired or have been terminated.

"***HSR Clearance Date***" means the earliest date on which the Parties have actual knowledge that all applicable waiting periods under the HSR Act with respect to the transactions contemplated under this Agreement have expired or have been terminated.

"***HSR Filing***" means filings by Biogen Idec and Isis with the United States Federal Trade Commission and the Antitrust Division of the United States Department of Justice of a Notification and Report Form for Certain Mergers and Acquisitions (as that term is defined in the HSR Act) with respect to the matters set forth in this Agreement, together with all required documentary attachments thereto.

"***HSR Termination Royalty***" has the meaning set forth in Section 10.2.3(b)(ii).

"***Incremental Tax Cost***" has the meaning set forth in Section 12.4.

"***IND***" means an Investigational New Drug Application (as defined in the Food, Drug and Cosmetic Act, as amended) filed with the FDA or its foreign counterparts.

"***IND-Enabling Toxicology Studies***" means the pharmacokinetic and toxicology studies required to meet the requirements for filing an IND.

"***Indemnitee***" has the meaning set forth in Section 9.3.

"***Initiation***" or "***Initiate***" means, with respect to any IND-Enabling Toxicology Study, dosing of the first animal subject in such IND-Enabling Toxicology Study and, with respect to any Clinical Study, dosing of the first human subject in such Clinical Study.

"***Integrated Development Plan***" or "***IDP***" has the meaning set forth in Section 5.1.2.

"***Isis***" has the meaning set forth in the Preamble of this Agreement.

"***Isis Breach Event***" has the meaning set forth in Section 10.4.4(a).

"***Isis Core Technology Patents***" means all Patent Rights owned, used, developed by, or licensed to Isis or its Affiliates, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term, claiming subject matter generally applicable to ASOs, other than Isis Product-Specific Patents or Isis Manufacturing and Analytical Patents. A list of Isis Core Technology Patents as of the Effective Date is set forth on SCHEDULE 8.2.5(a) attached hereto.

"***ISIS-DMPK$_{Rx}$ R&D Plan***" means the research and development plan attached hereto as APPENDIX 2.

"***Isis In-License Agreements***" has the meaning set forth in Section 6.8.1(a).

"***Isis Internal ASO Safety Database***" has the meaning set forth in Section 5.2.2.

"***Isis Know-How***" means any Know-How, including any Jointly-Owned Program Know-How and Isis Program Know-How, owned, used, developed by, or licensed to Isis or its Affiliates, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term. Isis Know-How does not include the Isis Manufacturing and Analytical Know-How.

"***Isis Manufacturing and Analytical Know-How***" means Know-How, including Jointly-Owned Program Know-How, that relates to the synthesis or analysis of the Product regardless of sequence or chemical modification, owned, used, developed by, or licensed to Isis or its Affiliates, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term. Isis Manufacturing and Analytical Know-How does not include the Isis Know-How.

"***Isis Manufacturing and Analytical Patents***" means Patent Rights, including Jointly-Owned Program Patents, that claim methods and materials used in the synthesis or analysis of the Product regardless of sequence or chemical modification, owned, used, developed by, or licensed to Isis or its Affiliates, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term. A list of Isis Manufacturing and

Analytical Patents as of the Effective Date is set forth on SCHEDULE 8.2.5(b) attached hereto. Isis Manufacturing and Analytical Patents do not include the Isis Product-Specific Patents or the Isis Core Technology Patents.

"***Isis Product-Specific Patents***" means all Product-Specific Patents, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term. A list of Isis Product-Specific Patents as of the Effective Date is set forth on SCHEDULE 8.2.5(c) attached hereto.

"***Isis Program Know-How***" has the meaning set forth in Section 7.1.2.

"***Isis Program Patents***" has the meaning set forth in Section 7.1.2.

"***Isis Supported Pass-Through Costs***" means [***].

"***Japan NDA***" or "***JNDA***" means the Japanese equivalent of an NDA filed with the Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto).

"***JNDA Approval***" means the Approval of a JNDA by the Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto) for the applicable Product in Japan.

"***Joint Patent Committee***" or "***JPC***" has the meaning set forth in Section 7.1.3(a).

"***Jointly-Owned Program Know-How***" has the meaning set forth in Section 7.1.2.

"***Jointly-Owned Program Patents***" has the meaning set forth in Section 7.1.2.

"***Jointly-Owned Program Technology***" has the meaning set forth in Section 7.1.2.

"***JSC***" has the meaning set forth in Section 1.2.1.

"***Know-How***" means inventions, technical information, know-how and materials, including technology, data, compositions, formulas, biological materials, assays, reagents, constructs, compounds, discoveries, procedures, processes, practices, protocols, methods, techniques, results of experimentation or testing, knowledge, trade secrets, skill and experience, in each case whether or not patentable or copyrightable.

"***Lead Party***" has the meaning set forth in Section 7.4.1.

"***Licensed Know-How***" means Isis Manufacturing and Analytical Know-How, and Isis Know-How. For clarity, Licensed Know-How does not include any Know-How covering formulation technology or delivery devices.

"***Licensed Patents***" means the Isis Product-Specific Patents, Isis Core Technology Patents, Isis Manufacturing and Analytical Patents and Isis' interest in Jointly-Owned Program Patents. For clarity, Licensed Patents do not include any Patent Rights claiming formulation technology or delivery devices unless such Patent Rights are included in the Jointly-Owned Program Patents.

"***Licensed Technology***" means any and all Licensed Patents, Licensed Know-How, and any trademarks described in Section 4.1.5, to the extent necessary or useful to Develop, register, Manufacture or Commercialize the Product. "*Licensed Technology*" expressly excludes all Patents Rights licensed to Isis under (i) [***], and (ii) [***].

"***Losses***" has the meaning set forth in Section 9.1.

"***MAA***" means a marketing authorization application filed with the EMA after completion of Clinical Studies to obtain Approval for the Product under the centralized European filing procedure or, if the centralized EMA filing procedure is not used, filed using the applicable procedures in any European Union country.

"***MAA Approval***" means the Approval of an MAA by the EMA for the Product in any country in the EU.

"***Major Market***" means any of the following countries: the United States, Japan, the United Kingdom, Germany, France, Italy and Spain.

"***Manufacture***" or "***Manufactured***" or "***Manufacturing***" means any activity involved in or relating to the manufacturing, quality control testing (including in-process, release and stability testing), releasing or packaging, for pre-clinical and clinical purposes, of API or the Product in finished form.

"***Manufacturing Agreement***" has the meaning set forth in Section 1.5.3.

"***Manufacturing License***" has the meaning set forth in Section 1.5.3.

"***Milestone Event***" means a Pre-Licensing Milestone Event or a Post-Licensing Milestone Event, as the case may be.

"***Minimum Third Party Payments***" means [***].

"***Myotonic Dystrophy-Type 1***" means an autosomal dominant genetic disease caused by a triplet expansion in 3'-UTR of DMPK. Myotonic Dystrophy-Type 1 is also known as "DM1."

"***NDA***" means a New Drug Application filed with the FDA after completion of Clinical Studies to obtain Approval for the Product in the United States.

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

"***Negotiation Period***" has the meaning set forth in Section 2.1.2.

"***Net Sales***" means the gross amount billed or invoiced on sales of the Product by Biogen Idec, its Affiliates and Sublicensees, less the following: (a) customary trade, quantity, or cash discounts to non-affiliated brokers or agents to the extent actually allowed and taken; (b) amounts repaid or credited by reason of rejection or return; (c) to the extent separately stated on purchase orders, invoices, or other documents of sale, any taxes or other governmental charges levied on the production, sale, transportation, delivery, or use of the Product which is paid by or on behalf of Isis; and (d) outbound transportation costs prepaid or allowed and costs of insurance in transit.

In any transfers of the Product between Biogen Idec, its Affiliates and Sublicensees, Net Sales are calculated based on the final sale of the Product to an independent Third Party. If Biogen Idec, its Affiliate or a Sublicensee receives non-monetary consideration for the Product, Net Sales are calculated based on the fair market value of that consideration. If Biogen Idec, its Affiliates or Sublicensees uses or disposes of the Product in the provision of a commercial service, the Product is sold and the Net Sales are calculated based on the sales price of the

Product to an independent Third Party during the same royalty period or, in the absence of sales, on the fair market value of the Product as determined by the Parties in good faith. Net Sales shall not include any transfers of supplies of the applicable Product for (i) use in clinical trials, pre-clinical studies or other research or development activities, or (ii) a *bona fide* charitable purpose; or (iii) a commercially reasonable sampling program.

"***New Third Party Licenses***" has the meaning set forth in Section 8.3.2.

"***Non-Breaching Party***" means the Party that believes the Breaching Party is in material breach of this Agreement.

"***Option***" has the meaning set forth in Section 3.1.3.

"***Option Deadline***" has the meaning set forth in Section 3.1.3.

"***Option Period***" has the meaning set forth in Section 2.1.1(a).

"***Other Pre-Option Activities***" has the meaning set forth in Section 1.5.4.

"***Other Pre-Option Costs***" has the meaning set forth in Section 1.5.4.

"***Panel Decision***" has the meaning set forth in Section 10.4.4(b).

"***Party***" or "***Parties***" means Biogen Idec and Isis individually or collectively.

"***Patent Costs***" means the reasonable fees and expenses paid to outside legal counsel, and filing, maintenance and other reasonable out-of-pocket expenses paid to Third Parties, incurred in connection with the Prosecution and Maintenance of Patent Rights.

"***Patent Rights***" means (a) patents, patent applications and similar government-issued rights protecting inventions in any country or jurisdiction however denominated, (b) all priority applications, divisionals, continuations, substitutions, continuations-in-part of and similar applications claiming priority to any of the foregoing, and (c) all patents and similar government-issued rights protecting inventions issuing on any of the foregoing applications, together with all registrations, reissues, renewals, re-examinations, confirmations, supplementary protection certificates, and extensions of any of (a), (b) or (c).

"***Permitted Licenses***" means (1) licenses granted by Isis before or after the Effective Date to any Third Party under the Isis Core Technology Patents, the Isis Manufacturing and Analytical Patents, or the Isis Manufacturing and Analytical Know-How (but not under the Isis Product-Specific Patents) to (a) use oligonucleotides (or supply oligonucleotides to end users) solely to conduct pre-clinical research, or (b) enable such Third Party to manufacture or formulate oligonucleotides, where (i) such Third Party is primarily engaged in providing contract manufacturing or services and is not primarily engaged in drug discovery, development or commercialization of therapeutics; and (ii) Isis does not assist such Third Party to identify, discover or make a Compound or Product; and (2) material transfer agreements with academic collaborators or non-profit institutions solely to conduct noncommercial research.

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

"***Pharmacovigilance Agreement***" has the meaning set forth in Section 5.2.1.

"***Phase 1 Trial***" means the first clinical study in human beings Initiated by Isis under the ISIS-DMPK$_{Rx}$ R&D Plan pursuant to an IND that has been filed with a Regulatory Authority in a Major Market or Canada. If Biogen Idec exercises the Option before Isis Initiates such a Phase 1 Trial, then the definition of "*Phase 1 Trial*" means the first clinical study of the Development Candidate in human beings Initiated by Biogen Idec, its Affiliate or its Sublicensee.

"***Phase 1 Trial Design***" means the Phase 1 Trial design set forth in the ISIS-DMPK$_{Rx}$ R&D Plan, which may be amended from time to time during the Agreement Term as mutually agreed in writing by the Parties (in consultation with the JSC).

"***Phase 2 Trial***" means a Clinical Study that is intended to explore the feasibility, safety, dose ranging or efficacy of such product, that is prospectively designed to generate sufficient data (if successful) to commence a Phase 3 Clinical Trial (or foreign equivalent) of such product, as further defined in 21 C.F.R. 312.21(b) or the corresponding regulation in jurisdictions other than the United States.

"***Phase 3 Trial***" means as to a specific pharmaceutical product, a pivotal Clinical Study in humans performed to gain evidence with statistical significance of the efficacy of such product in a target population, and to obtain expanded evidence of safety for such product that is needed to evaluate the overall benefit-risk relationship of such product, to form the basis for approval of an NDA by a Regulatory Authority and to provide an adequate basis for physician labeling, as described in 21 C.F.R. 312.21(c), as amended from time to time, or the corresponding regulation in jurisdictions other than the United States.

"***Phase 4 Trial***" means (a) any Clinical Study conducted to satisfy a requirement of a Regulatory Authority in order to maintain a Regulatory Approval or (b) any Clinical Study conducted after the first Regulatory Approval in the same disease state for which a Product received Regulatory Approval other than for purposes of obtaining Regulatory Approval.

"***PoC Data Package***" means, with respect to the Product, [***], (iv) copies of all filings submitted to Regulatory Authorities regarding the Product, (v) a summary of the patent status relating to the Product, and (vi) a summary of any Third Party Obligations Isis believes relate to the Product.

"***PoC Trial***" means the clinical study described in the ISIS-DMPK$_{Rx}$ R&D Plan, as such plan may be amended from time to time in accordance with this Agreement, as a [***]." If Biogen Idec exercises the Option before Isis Initiates such a PoC Trial, then the definition of "*PoC Trial*" means the [***] by Biogen Idec, its Affiliate or its Sublicensee.

"***PoC Trial Completion Notice***" has the meaning set forth in Section 3.1.2.

"***PoC Trial Design***" means the PoC Trial design set forth in the ISIS-DMPK$_{Rx}$ R&D Plan, which may be amended from time to time during the Agreement Term as mutually agreed in writing by the Parties (in consultation with the JSC).

"***Post-Licensing Milestone Event***" has the meaning set forth in Section 6.4.

"***Post-Termination Development Candidate***" has the meaning set forth in Section 10.2.8.

"***Pre-Clinical Studies***" means *in vitro* and *in vivo* studies of the Product, not in humans, including those studies conducted in whole animals and other test systems, designed to determine the toxicity, bioavailability, and pharmacokinetics of the Product and whether the Product has a desired effect.

"***Pre-Licensing Milestone Event***" has the meaning set forth in Section 6.2.

"***Prior Agreements***" means the agreements listed on SCHEDULE 8.2.8 attached hereto.

"***Proceeding***" means an action, suit or proceeding.

"***Product***" means a finished drug product containing a Compound as an active pharmaceutical ingredient.

"***Product-Specific Patents***" means Patent Rights Controlled by a Party or any of its Affiliates on or after the Effective Date, including any Program Patents, claiming (i) the specific composition of matter of the Product, or (ii) methods of using the Product as a prophylactic or therapeutic; *provided however*, Patent Rights Controlled by Isis or any of its Affiliates that (y) include claims that are directed to subject matter applicable to ASOs in general, or (z) include an ASO, the sequence of which targets the RNA that encodes DMPK and the RNA of a gene that does not encode DMPK, will not be considered Product-Specific Patents, and in the case of (y) and (z), such Patent Rights will be considered Isis Core Technology Patents.

"***Program Patents***" has the meaning set forth in Section 7.1.2.

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

"***Receiving Party***" has the meaning set forth in Section 11.1.

"***Reduced Royalty Period***" has the meaning set forth in Section 6.6.2(e).

"***Regulatory Approval***" means the approval necessary for the commercial manufacture, distribution, marketing, promotion, offer for sale, use, import, export, and sale of a pharmaceutical product in a jurisdiction regulated by a Regulatory Authority.

"***Regulatory Authority***" means any governmental authority, including the FDA, EMA or Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto), that has responsibility for granting any licenses or approvals or granting pricing or reimbursement approvals necessary for the marketing and sale of the Product in any country.

"***Research***" means conducting the research activities with Compounds as set forth in the ISIS-DMPK$_{Rx}$ R&D Plan, including pre-clinical research and lead optimization, *but specifically excluding* Development and Commercialization. When used as a verb, "*Researching*" means to engage in Research.

[***]

"***Reverse Royalties***" has the meaning set forth in Section 6.7.1.

"***RMC***" means Isis' Research Management Committee, or any successor committee.

"***ROFN Period***" has the meaning set forth in Section 2.1.2.

"***ROFN Termination Event***" has the meaning set forth in Section 2.1.2.

"***Royalty Quotient***" has the meaning set forth in Section 6.6.2(c).

"***Service Provider***" means the Third Party(ies) conducting the original and revised studies under the ISIS-DMPK$_{Rx}$ R&D Plan.

"***Setoff Amount***" has the meaning set forth in Section 10.4.4(b).

"***Setoff Dispute***" has the meaning set forth in Section 10.4.4(b).

"***Setoff Dispute Notice***" has the meaning set forth in Section 10.4.4(b).

"***SMN Agreement***" has the meaning set forth in Section 1.2.1.

"***Specific Performance Milestone Event***" has the meaning set forth in Section 5.1.1.

"***Step-In Party***" has the meaning set forth in Section 7.4.1.

"***Sublicensee***" means a Third Party to whom a Party or its Affiliates or Sublicensees has granted a sublicense or license under any Licensed Technology or Biogen Idec Technology, as the case may be, licensed to such Party in accordance with the terms of this Agreement.

"***Subsequent DMPK Deal***" has the meaning set forth in Section 10.2.3(b)(i).

"***Superior Patent Right***" has the meaning set forth in Section 7.2.4(c).

"***Third Party***" means a Person or entity other than the Parties or their respective Affiliates.

"***Third Party Obligations***" means any financial and non-financial encumbrances, obligations, restrictions, or limitations imposed by an agreement between Isis and a Third Party (including the Isis In-License Agreements) that relate to the Product, DMPK, including field or territory restrictions, covenants, milestone payments, diligence obligations, sublicense revenue, royalties, or other payments.

"***Trial Court***" has the meaning set forth in Section 10.4.4(b).

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

[***]

[***]

"***Valid Claim***" means a claim (i) of any issued, unexpired United States or foreign Patent Right, which will not, in the country of issuance, have been donated to the public, disclaimed, nor held invalid or unenforceable by a court of competent jurisdiction in an unappealed or unappealable decision, or (ii) of any United States or foreign patent application within a Patent Right, which will not, in the country in question, have been cancelled, withdrawn, abandoned nor been pending for more than seven years, not including in calculating such seven-year period of time in which such application is in interference or opposition or similar proceedings or time in which a decision of an examiner is being appealed. Notwithstanding the foregoing, on a country-by-country basis, a patent application pending for more than seven years will not be considered to have any Valid Claim for purposes of this Agreement unless and until a patent meeting the criteria set forth in clause (i) above with respect to such application issues.

APPENDIX 2

ISIS-DMPK$_{Rx}$ R&D Plan

[***]

APPENDIX 3

Development Candidate Checklist

[***]

SCHEDULE 1.2.1

JSC GOVERNANCE

(a) The JSC will determine the JSC operating procedures, including frequency of meetings (at least quarterly), location of meetings, and responsibilities for agendas and minutes. The JSC will codify these operating procedures in the written minutes of the first meeting.

(b) The JSC may hold meetings in person or by audio or video conference as determined by the JSC; but at least two meetings per year will be in person (one held at Isis' facilities, and the other held at Biogen Idec's facilities in the U.S.). Alliance Managers will attend JSC meetings as participating non-members. In addition, upon prior approval of the other Party, each Party may invite its employees or consultants to attend JSC meetings, including any subject matter expert(s) with valuable knowledge of DMPK or Myotonic Dystrophy-Type 1.

(c) The co-chairs will be responsible for ensuring that activities occur as set forth in this Agreement, including ensuring that JSC meetings occur, JSC recommendations are properly reflected in the minutes, and any dispute is given prompt attention and resolved in accordance with Section 1.2.3, Section 7.1.3 and Section 12.1, as applicable.

(d) The JSC members from the same Party will collectively have one vote. The JSC will strive to make recommendations with approval of both Isis members and Biogen Idec members, and record such recommendations in the minutes of the applicable JSC meeting.

(e) The JSC may form subcommittees and working groups as it determines in order to carry out its activities under this Agreement, all of which will dissolve when the JSC dissolves.

SCHEDULE 1.2.2(b)

Other Potential Development Activities for Consideration

[***]

SCHEDULE 1.2.6

Alliance Management Activities

Each Alliance Manager is responsible for:

(a) Promoting the overall health of the relationship between the Parties;

(b) Developing a mutually agreed alliance launch plan covering any activities and systems that the Parties need to implement within the first 100 days after the Effective Date to support the ISIS-DMPK$_{Rx}$ R&D Plan;

(c) Organizing JSC meetings, including agendas, drafting minutes, and publishing final minutes;

(d) Supporting the co-chairs of the JSC with organization of meetings, information exchange, meeting minutes, and facilitating dispute resolution as necessary;

(e) Preparing status and progress reports on the above as determined necessary by the JSC;

(f) Ensuring compliance in maintaining the Isis Internal ASO Safety Database as outlined in Section 5.2;

(g) Ensuring proper approval of publications prior to submission as required in Section 11.4; and

(h) Understanding and communicating the components contained in the relationship-management document provided by Isis to Biogen Idec, to assist Biogen Idec in understanding and complying with the contractual obligations under the Isis In-License Agreements after Option exercise.

SCHEDULE 4.5.3

Isis' Fully Absorbed Cost of Goods Methodology
Cost Estimate of API Cost per Kilogram
(OOO's)

[***]

SCHEDULE 5.1.1

Biogen Idec's Development and Commercialization Activities and Specific Performance Milestone Events

[***]

92

SCHEDULE 6.6.2(f)

Royalty Calculation Examples

[***]

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SCHEDULE 6.6.2(g)

Allocation of Net Sales

[***]

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SCHEDULE 6.8.1

Isis In-License Agreements

(Relevant to the ISIS-DMPK$_{Rx}$ R&D Plan as of the Effective Date)

[***]

95

SCHEDULE 8.2.5(a)

Isis Core Technology Patents

[***]

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SCHEDULE 8.2.5(b)

Isis Manufacturing and Analytical Patents

[***]

97

SCHEDULE 8.2.5(c)

Isis Product-Specific Patents

[***]

SCHEDULE 8.2.8

Prior Agreements

[***]

SCHEDULE 10.4.4(b)

Advisory Panel Regarding Setoff Disputes

[***]

SCHEDULE 12.1.2

Mediation

1. Mediation.

1.1. If a Dispute cannot be resolved pursuant to Section 12.1.1 of the Agreement (Escalation), the Parties agree to try in good faith to resolve any such Dispute by non-binding mediation administered by the American Arbitration Association (the "***AAA***") in accordance with its Commercial Mediation Procedures then in effect (the "***Procedures***"), as modified by this Section 1.1 of this SCHEDULE 12.1.2. The mediation will be conducted by a single mediator appointed by agreement of the Parties, within 15 days after either Party notifies the other Party of its intention to mediate such Dispute, or failing such agreement, appointed by the AAA in accordance with the Procedures; *provided*, that in either case the mediator will be a retired Delaware state or federal judge. Unless otherwise mutually agreed upon by the Parties, the mediation proceedings will be conducted in Dover, Delaware. The Parties agree that they will share equally the costs and expenses of the mediation; *provided*, that each Party will bear its own attorneys' fees and associated costs and expenses. The mediation conference will be held within 30 days after appointment of the mediator, and will last no more than two consecutive days unless otherwise mutually agreed upon by the Parties. Any resolution of a Dispute by mediation pursuant to this Section 1.1 of these mediation procedures will be in writing and signed by duly authorized representatives of both Parties.

1.2. If the Parties cannot resolve a Dispute in accordance with Section 1.1 of this SCHEDULE 12.1.2, then such Dispute will be resolved by the Parties in accordance with Section 12.2 of the Agreement (Governing Law; Jurisdiction; Venue; Service of Process).

SCHEDULE 12.5

Applicable License Fee Payments in Change of Control

[***]

Exhibit 10.2

THIRD AMENDMENT TO LOAN AGREEMENT

THIS THIRD AMENDMENT TO LOAN AGREEMENT (this "Third Amendment") is made and entered into as of June 24, 2012, between ISIS PHARMACEUTICALS, INC., a Delaware corporation (together with its successors and assigns, "Borrower"), and RBS ASSET FINANCE, INC., a New York corporation (together with its successors and assigns, "Lender").

RECITALS

A. Lender and Borrower have previously entered into a Loan Agreement dated as of October 15, 2008 a First Amendment to Loan Agreement dated as of September 30, 2009, and a Second Amendment to Loan Agreement dated as of November 15, 2010 (collectively, the "Agreement").

B. Lender and Borrower wish to amend the Agreement as provided herein.

NOW, THEREFORE, in consideration of the premises and the mutual covenants and agreements herein contained, and for other good and valuable consideration, the receipt of which is hereby acknowledged, it is hereby agreed as follows:

1. The Agreement is amended as follows:

(i) The definitions of the following terms set forth in Schedule I to the Agreement are hereby amended to have the meanings set forth below:

"Financial Statements" means the audited financial statement of Borrower and each Guarantor for their fiscal years ended December 31, 2011.

"Maximum Principal Amount" means Thirty-Three Million Four-Hundred Thousand Dollars and *00/100* ($33,400,000.00)

"Fixed Rate" means, with respect to each Loan and each Note, a rate per annum equal to the sum of (i) the notional rate per annum for a fixed rate payer under a 3 year interest rate swap on the day that is two Business Days prior to the applicable Closing Date plus (ii) (a) 3.50% or (b) such other amount as may be mutually agreed upon by Lender and Borrower, which rate will be set forth in such Note.

"Scheduled Commitment Termination Date" means April 15, 2014.

(ii) The definition of the following term set forth in ARTICLE I: DEFINITIONS AND ACCOUNTING TERMS Section 1.01 Defined Terms to the Agreement is hereby amended to have the meaning set forth below:

"Commitment Termination Date" means the earliest of (a) the date on which the aggregate Original Principal Amount of all Loans equals the Maximum Principal Amount, (b) the Scheduled Commitment Termination Date, (c) the date that an Event of Default described in subsection (i) of Section 7.01 occurs or (d) the date on which Lender elects to terminate the Commitment following (i) an Event of Default or (ii) the occurrence of a material adverse change in the business, condition (financial or otherwise), operations, markets, properties, performance, financial reporting, or financial condition of Borrower or any Guarantor or in Borrower's ability to comply with any Loan Document, since the date of this Agreement as determined by Lender, in its sole discretion and in good faith or (b) a material impairment of the ability of Borrower to perform its Obligations under or remain in compliance with each Loan Document, or (c) a materially adverse effect on the validity or enforceability of any Loan Document or the rights and remedies available to Lender thereunder.

2. First Amendment to Loan Agreement added the following Negative Covenant in Section 6.02 sub-section (f):

"(f) Borrower shall maintain a depository account with RBS Citizens Bank, N.A. as with a balance of at least Two Hundred Fifty-Thousand Dollars and 00/100 ($250,000.00) until all Obligations of Borrower to Lender under the Agreement are indefeasibly paid in full."

Lender acknowledges that as of the date of this Agreement Borrower's account number 1315925467 with RBS Citizens Bank, NA complies with this covenant.

3. Borrower agrees to provide Lender, within five (5) business days of receipt by Borrower, with a copy of any notice received by Borrower from BMR-GAZELLE LP (together with any successor thereto, the "Landlord") related to or asserting any default or Event of Default by the Borrower under the terms and provisions of, or otherwise cancelling or terminating, that certain Lease Agreement dated as of March 30, 2010 between Landlord and Borrower (as amended from time to time, the "Lease"). Additionally, in the event that the Borrower elects to terminate such Lease, Borrower shall provide written notice to the Lender contemporaneous with delivery of such termination notice to the Landlord. The obligations under this paragraph 3 will terminate once all Obligations of Borrower to Lender under the Agreement are indefeasibly paid in full.

3. This Third Amendment may be executed in several counterparts, each of which shall be an original and all of which shall constitute but one and the same instrument.

4. All other terms and conditions of the Agreement not specifically amended by this Third Amendment shall remain in full force and effect and are hereby ratified and confirmed by Lender and Borrower.

5. This Third Amendment shall be governed by the law of the State of Illinois (without regard to the confiict of-laws principles thereof).

[REMAINDER OF PAGE INTENTIONALLY LEFT BLANK; EXECUTION PAGE FOLLOWS]

IN WITNESS WHEREOF, the parties hereto have executed this Third Amendment in their respective corporate names by their duly authorized officers, all as of the date first written above.

Lender: RBS ASSET FINANCE, INC., a New York corporation
By /s/ Jeffrey P. Lanigan
Name Jeffrey P. Lanigan
Title Assistant Vice President

Borrower: ISIS PHARMACEUTICALS, INC., a Delaware corporation
By /s/ B. Lynne Parshall
Name B. Lynne Parshall
Title COO & CFO

[EXECUTION PAGE OF THIRD AMENDMENT TO LOAN AGREEMENT]

ISIS PHARMACEUTICALS, INC.
RESTRICTED STOCK UNIT GRANT NOTICE
(AMENDED & RESTATED 2002 NON-EMPLOYEE DIRECTOR'S STOCK OPTION PLAN)

Isis Pharmaceuticals, Inc. (the ***"Company"***), pursuant to its Amended & Restated 2002 Non-Employee Director's Stock Option Plan (the ***"Plan"***), hereby awards to Participant a Restricted Stock Unit Award for the number of stock units set forth below (the ***"Award"***). The Award is subject to all of the terms and conditions as set forth herein; and in the Plan and the Restricted Stock Unit Agreement, both of which are attached hereto and incorporated herein in their entirety. Capitalized terms not otherwise defined herein shall have the meanings set forth in the Plan or the Restricted Stock Unit Agreement. In the event of any conflict between the terms in the Award and the Plan, the terms of the Plan shall control.

Participant:
Date of Grant:
Vesting Commencement Date:
Number of Stock Units Subject to Award:
Consideration: Participant's Services

Vesting Schedule: 25% of the Stock Units subject to this Award will vest on each of the first, second, third, and fourth anniversary of the Vesting Commencement Date. Notwithstanding the foregoing, vesting shall terminate upon the Participant's termination of Continuous Service.

Issuance Schedule: The shares of Common Stock to be issued in respect of the Award will be issued in accordance with the issuance schedule set forth in Section 6 of the Restricted Stock Unit Agreement.

Additional Terms/Acknowledgements: The undersigned Participant acknowledges receipt of, and understands and agrees to, this Restricted Stock Unit Grant Notice, the Restricted Stock Unit Agreement and the Plan. Participant further acknowledges that as of the Date of Grant, this Restricted Stock Unit Grant Notice, the Restricted Stock Unit Agreement and the Plan set forth the entire understanding between Participant and the Company regarding the Award and supersedes all prior oral and written agreements on that subject.

ISIS PHARMACEUTICALS, INC.

By: _____
Signature

Title: _____

Date: _____

PARTICIPANT:

_____
Signature

Date: _____

ATTACHMENTS: Restricted Stock Unit Agreement, Amended & Restated 2002 Non-Employee Director's Stock Option Plan

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ISIS PHARMACEUTICALS, INC.
AMENDED & RESTATED 2002 NON-EMPLOYEE DIRECTOR'S
STOCK OPTION PLAN

RESTRICTED STOCK UNIT AGREEMENT

Pursuant to the Restricted Stock Unit Grant Notice ("***Grant Notice***") and this Restricted Stock Unit Agreement and in consideration of your services, Isis Pharmaceuticals, Inc. (the "***Company***") has awarded you a Restricted Stock Unit Award (the "***Award***") under its Amended & Restated 2002 Non-Employee Director's Stock Option Plan (the "***Plan***"). Your Award is granted to you effective as of the Date of Grant set forth in the Grant Notice for this Award. This Restricted Stock Unit Award Agreement shall be deemed to be agreed to by the Company and you upon the earlier of (i) signing (or electronic acceptance) by you of the Restricted Stock Unit Grant Notice to which it is attached, and (ii) your receipt of shares of Common Stock under this Restricted Stock Unit Agreement. Capitalized terms not explicitly defined in this Restricted Stock Unit Agreement shall have the same meanings given to them in the Plan or the Grant Notice, as applicable. In the event of any conflict between the terms in this Restricted Stock Unit Agreement and the Plan, the terms of the Plan shall control. The details of your Award, in addition to those set forth in the Grant Notice and the Plan, are as follows.

1. GRANT OF THE AWARD. This Award represents the right to be issued on a future date the number of shares of the Company's Common Stock that is equal to the number of stock units indicated in the Grant Notice (the "***Stock Units***"). As of the Date of Grant, the Company will credit to a bookkeeping account maintained by the Company for your benefit (the "***Account***") the number of Stock Units subject to the Award. This Award was granted in consideration of your services to the Company. Except as otherwise provided herein, you will not be required to make any payment to the Company (other than past and future services to the Company) with respect to your receipt of the Award, the vesting of the Stock Units or the delivery of the Common Stock to be issued in respect of the Award.

2. VESTING.

(a) In General. Subject to the limitations contained herein, your Award will vest, if at all, in accordance with the vesting schedule provided in the Grant Notice, provided that vesting will cease upon the termination of your Continuous Service. Upon such termination of your Continuous Service, the Stock Units credited to the Account that were not vested on the date of such termination will be forfeited at no cost to the Company and you will have no further right, title or interest in the Stock Units or the shares of Common Stock to be issued in respect of the Award.

3. NUMBER OF SHARES.

(a) The number of Stock Units subject to your Award may be adjusted from time to time for Capitalization Adjustments, as provided in the Plan.

(b) Any additional Stock Units that become subject to the Award pursuant to this Section 3 and Section 7, if any, shall be subject, in a manner determined by the Board, to the same forfeiture restrictions, restrictions on transferability, and time and manner of delivery as applicable to the other Stock Units covered by your Award.

(c) Notwithstanding the provisions of this Section 3, no fractional shares or rights for fractional shares of Common Stock shall be created pursuant to this Section 3. The Board shall, in its discretion, determine an equivalent benefit for any fractional shares or fractional shares that might be created by the adjustments referred to in this Section 3.

4. SECURITIES LAW COMPLIANCE. You may not be issued any shares in respect of your Award unless either (i) the shares are registered under the Securities Act; or (ii) the Company has determined that such issuance would be exempt from the registration requirements of the Securities Act. Your Award also must comply with other applicable laws and regulations governing the Award, and you will not receive such shares if the Company determines that such receipt would not be in material compliance with such laws and regulations.

5. TRANSFER RESTRICTIONS. Prior to the time that shares of Common Stock have been delivered to you, you may not transfer, pledge, sell or otherwise dispose of this Award or the shares issuable in respect of your Award, except as expressly provided in this Section 5. For example, you may not use shares that may be issued in respect of your Award as security for a loan. The restrictions on transfer set forth herein will lapse upon delivery to you of shares in respect of your vested Award.

(a) Death. Your Award is transferable by will and by the laws of descent and distribution. In addition, upon receiving written permission from the Board or its duly authorized designee, you may, by delivering written notice to the Company, in a form provided by or otherwise satisfactory to the Company and any broker designated by the Company to effect transactions under the Plan, designate a third party who, in the event of your death, shall thereafter be entitled to receive any distribution of Common Stock or other consideration to which you were entitled at the time of your death pursuant to this Agreement. In the absence of such a designation, your executor or administrator of your estate shall be entitled to receive, on behalf of your estate, such Common Stock or other consideration.

(b) Certain Trusts. Upon receiving written permission from the Board or its duly authorized designee, you may transfer your Award to a trust if you are considered to be the sole beneficial owner (determined under Section 671 of the Code and applicable state law) while the Award is held in the trust, provided that you and the trustee enter into transfer and other agreements required by the Company.

(c) Domestic Relations Orders. Upon receiving written permission from the Board or its duly authorized designee, and provided that you and the designated transferee enter into transfer and other agreements required by the Company, you may transfer your Award or your right to receive the distribution of Common Stock or other consideration thereunder, pursuant to a domestic relations order that contains the information required by the Company to effectuate the transfer. You are encouraged to discuss the proposed terms of any division of this Award with the Company prior to finalizing the domestic relations order to help ensure the required information is contained within the domestic relations order.

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6. DATE OF ISSUANCE.

(a) If the Award is exempt from application of Section 409A of the Code and the regulations and other guidance thereunder and any state law of similar effect (collectively ***"Section 409A"***), the Company will deliver to you a number of shares of the Company's Common Stock equal to the number of vested Stock Units subject to your Award, including any additional Stock Units received pursuant to Section 3 above that relate to those vested Stock Units on the applicable vesting date(s). However, if a scheduled delivery date falls on a date that is not a business day, such delivery date shall instead fall on the next following business day. Notwithstanding the foregoing, in the event that (i) you are subject to the Company's policy permitting officers and directors to sell shares only during certain "window" periods, in effect from time to time (the "***Policy***") or you are otherwise prohibited from selling shares of the Company's Common Stock in the public market and any shares covered by your Award are scheduled to be delivered on a day (the "***Original Distribution Date***") that does not occur during an open "window period" applicable to you or a day on which you are permitted to sell shares of the Company's common stock pursuant to a written plan that meets the requirements of Rule 10b5-1 under the Exchange Act, in each case as determined by the Company in accordance with the Policy, or does not occur on a date when you are otherwise permitted to sell shares of the Company's common stock on the open market, and (ii) the Company elects not to satisfy its tax withholding obligations (if any) by withholding shares from your distribution, then such shares shall not be delivered on such Original Distribution Date and shall instead be delivered on the first business day of the next occurring open "window period" applicable to you pursuant to such policy (regardless of whether you are still providing continuous services at such time) or the next business day when you are not prohibited from selling shares of the Company's Common Stock in the open market, but in no event later than the fifteenth day of the third calendar month of the calendar year following the calendar year in which the shares covered by the Award vest. Delivery of the shares pursuant to the provisions of this Section 6(a) is intended to comply with the requirements for the short-term deferral exemption available under Treasury Regulation 1.409A-1(b)(4) and shall be construed and administered in such manner. The form of such delivery of the shares (*e.g.*, a stock certificate or electronic entry evidencing such shares) shall be determined by the Company.

(b) The provisions of this Section 6(b) are intended to apply if the Award is subject to Section 409A because of the terms of a severance arrangement or other agreement between you and the Company, if any, that provides for acceleration of vesting of the Award upon your separation from service (as such term is defined in section 409A(a)(2)(A)(i) of the Code and applicable guidance thereunder ("***Separation From Service***") and such severance benefit does not satisfy the requirements for an exemption from application of Section 409A provided under Treasury Regulations Sections 1.409A-1(b)(4) or 1.409A-1(b)(9) ("***Non-Exempt Severance Arrangement***"). If the Award is subject to and not exempt from application of Section 409A due to application of a Non-Exempt Severance Arrangement, the following provisions in this Section 6(b) shall supersede anything to the contrary in Section 6(a).

(i) If the Award vests in ordinary course during your Continuous Service in accordance with the vesting schedule set forth in the Grant Notice, in no event will the shares to be issued in respect of your Award be issued any later than the later of: (i) December 31st of the calendar year that includes the applicable vesting date, or (ii) the 60th day that follows the applicable vesting date.

(ii) If the Award accelerates vesting under the terms of your Non-Exempt Severance Arrangement in connection with your Separation From Service, and such vesting acceleration provisions of your Non-Exempt Severance Arrangement were in effect as of the date of grant of the Award and therefore part of the terms of the Award as of the date of grant, then the shares will be earlier issued in respect of your Award upon your Separation From Service in accordance with the terms of the Non-Exempt Severance Arrangement, but in no event later than the 60th day that follows the date of your Separation From Service. However, if at the time the shares would otherwise be issued you are subject to the distribution limitations contained in section 409A of the Code applicable to "specified employees" as defined in section 409A(a)(2)(B)(i) of the Code and applicable guidance thereunder, such share issuances shall not be made before the date which is six months following the date of your Separation From Service, or, if earlier, the date of your death that occurs within such six month period.

(iii) If the Award accelerates vesting under the terms of your Non-Exempt Severance Arrangement in connection with your Separation From Service, and such vesting acceleration provisions of your Non-Exempt Severance Arrangement were not in effect as of the date of grant of the Award and therefore not a part of the terms of the Award on the date of grant, then such acceleration of vesting of the Award shall not accelerate the issuance date of the shares, but the shares shall instead be issued on the same schedule as set forth on the Grant Notice as if they had vested in ordinary course during your Continuous Service, notwithstanding the vesting acceleration of the Award. Such issuance schedule is intended to satisfy the requirements of payment on a specified date or pursuant to a fixed schedule, as provided under Treas. Reg. 1.409A-3(a)(4).

(c) The provisions in this Agreement for delivery of the shares in respect of the Award are intended either to comply with the requirements of Section 409A or to provide a basis for exemption from such requirements so that the delivery of the shares will not trigger the additional tax imposed under Section 409A, and any ambiguities herein will be so interpreted.

7. DIVIDENDS. You shall be entitled to receive payments equal to any cash dividends and other distributions paid with respect to a corresponding number of shares to be issued in respect of the Stock Units covered by your Award, provided that if any such dividends or distributions are paid in shares, the Fair Market Value of such shares shall be converted into additional Stock Units covered by the Award, and further provided that such additional Stock Units shall be subject to the same forfeiture restrictions and restrictions on transferability as apply to the Stock Units subject to the Award with respect to which they relate.

8. RESTRICTIVE LEGENDS. The shares issued in respect of your Award shall be endorsed with appropriate legends determined by the Company.

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9. AWARD NOT A SERVICE CONTRACT.

(a) Your Continuous Service with the Company or an Affiliate is not for any specified term and may be terminated by you or by the Company or an Affiliate at any time, for any reason, with or without cause and with or without notice. Nothing in this Restricted Stock Unit Agreement (including, but not limited to, the vesting of your Award pursuant to the schedule set forth in Section 2 herein or the issuance of the shares in respect of your Award), the Plan or any covenant of good faith and fair dealing that may be found implicit in this Restricted Stock Unit Agreement or the Plan shall: (i) confer upon you any right to continue in the employ of, or affiliation with, the Company or an Affiliate; (ii) constitute any promise or commitment by the Company or an Affiliate regarding the fact or nature of future positions, future work assignments, future compensation or any other term or condition of employment or affiliation; (iii) confer any right or benefit under this Restricted Stock Unit Agreement or the Plan unless such right or benefit has specifically accrued under the terms of this Agreement or Plan; or (iv) deprive the Company of the right to terminate you at will and without regard to any future vesting opportunity that you may have.

(b) By accepting this Award, you acknowledge and agree that the right to continue vesting in the Award pursuant to the schedule set forth in Section 2 is earned only by continuing as an employee, director or consultant at the will of the Company (not through the act of being hired, being granted this Award or any other award or benefit) and that the Company has the right to reorganize, sell, spin-out or otherwise restructure one or more of its businesses or Affiliates at any time or from time to time, as it deems appropriate (a "reorganization"). You further acknowledge and agree that such a reorganization could result in the termination of your Continuous Service, or the termination of Affiliate status of your employer and the loss of benefits available to you under this Restricted Stock Unit Agreement, including but not limited to, the termination of the right to continue vesting in the Award. You further acknowledge and agree that this Restricted Stock Unit Agreement, the Plan, the transactions contemplated hereunder and the vesting schedule set forth herein or any covenant of good faith and fair dealing that may be found implicit in any of them do not constitute an express or implied promise of continued engagement as an employee or consultant for the term of this Agreement, for any period, or at all, and shall not interfere in any way with your right or the Company's right to terminate your Continuous Service at any time, with or without cause and with or without notice.

10. WITHHOLDING OBLIGATIONS.

(a) On or before the time you receive a distribution of the shares subject to your Award, or at any time thereafter as requested by the Company, you hereby authorize any required withholding (if any) from the Common Stock issuable to you and/or otherwise agree to make adequate provision in cash for any sums required to satisfy the federal, state, local and foreign tax withholding obligations (if any) of the Company or any Affiliate which arise in connection with your Award (the "***Withholding Taxes***"). Additionally, the Company may, in its sole discretion, satisfy all or any portion of the Withholding Taxes obligation relating to your Award by any of the following means or by a combination of such means: (i) withholding from any compensation otherwise payable to you by the Company; (ii) causing you to tender a cash payment; or (iii) withholding shares of Common Stock from the shares of Common Stock issued or otherwise issuable to you in connection with the Award with a Fair Market Value (measured

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as of the date shares of Common Stock are issued to pursuant to Section 6) equal to the amount of such Withholding Taxes; provided, however, that the number of such shares of Common Stock so withheld shall not exceed the amount necessary to satisfy the Company's required tax withholding obligations

using the minimum statutory withholding rates for federal, state, local and foreign tax purposes, including payroll taxes, that are applicable to supplemental taxable income.

(b) Unless the tax withholding obligations of the Company and/or any Affiliate are satisfied, the Company shall have no obligation to deliver to you any Common Stock.

(c) In the event the Company's obligation to withhold arises prior to the delivery to you of Common Stock or it is determined after the delivery of Common Stock to you that the amount of the Company's withholding obligation was greater than the amount withheld by the Company, you agree to indemnify and hold the Company harmless from any failure by the Company to withhold the proper amount.

(d) If specified in your Grant Notice and permitted by the Company, you may direct the Company to withhold shares of Common Stock with a Fair Market Value (measured as of the date shares of Common Stock are issued pursuant to Section 6) equal to the amount of such Withholding Taxes; provided, however, that the number of such shares of Common Stock so withheld shall not exceed the amount necessary to satisfy the Company's required tax withholding obligations using the minimum statutory withholding rates for federal, state, local and foreign tax purposes, including payroll taxes, that are applicable to supplemental taxable income.

11. UNSECURED OBLIGATION. Your Award is unfunded, and as a holder of a vested Award, you shall be considered an unsecured creditor of the Company with respect to the Company's obligation, if any, to issue shares pursuant to this Agreement. You shall not have voting or any other rights as a stockholder of the Company with respect to the shares to be issued pursuant to this Agreement until such shares are issued to you pursuant to Section 6 of this Agreement. Upon such issuance, you will obtain full voting and other rights as a stockholder of the Company. Nothing contained in this Agreement, and no action taken pursuant to its provisions, shall create or be construed to create a trust of any kind or a fiduciary relationship between you and the Company or any other person.

12. OTHER DOCUMENTS. You hereby acknowledge receipt or the right to receive a document providing the information required by Rule 428(b)(1) promulgated under the Securities Act, which includes the Plan prospectus. In addition, you acknowledge receipt of the Company's insider-trading policy and agree that you may sell shares only in compliance with such policy, in effect from time to time.

13. NOTICES. Any notices provided for in your Award or the Plan shall be given in writing and shall be deemed effectively given upon receipt or, in the case of notices delivered by the Company to you, five days after deposit in the United States mail, postage prepaid, addressed to you at the last address you provided to the Company. Notwithstanding the foregoing, the Company may, in its sole discretion, decide to deliver any documents related to participation in

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the Plan and this Award by electronic means or to request your consent to participate in the Plan by electronic means. You hereby consent to receive such documents by electronic delivery and, if requested, to agree to participate in the Plan through an on-line or electronic system established and maintained by the Company or another third party designated by the Company.

14. MISCELLANEOUS.

(a) The rights and obligations of the Company under your Award shall be transferable to any one or more persons or entities, and all covenants and agreements hereunder shall inure to the benefit of, and be enforceable by the Company's successors and assigns. Your rights and obligations under your Award may only be assigned with the prior written consent of the Company.

(b) You agree upon request to execute any further documents or instruments necessary or desirable in the sole determination of the Company to carry out the purposes or intent of your Award.

(c) You acknowledge and agree that you have reviewed your Award in its entirety, have had an opportunity to obtain the advice of counsel prior to executing and accepting your Award, and fully understand all provisions of your Award.

(d) This Agreement shall be subject to all applicable laws, rules, and regulations, and to such approvals by any governmental agencies or national securities exchanges as may be required.

(e) All obligations of the Company under the Plan and this Agreement shall be binding on any successor to the Company, whether the existence of such successor is the result of a direct or indirect purchase, merger, consolidation, or otherwise, of all or substantially all of the business and/or assets of the Company.

15. GOVERNING PLAN DOCUMENT. Your Award is subject to all the provisions of the Plan, the provisions of which are hereby made a part of your Award, and is further subject to all interpretations, amendments, rules and regulations which may from time to time be promulgated and adopted pursuant to the Plan. Except as expressly provided herein, in the event of any conflict between the provisions of your Award and those of the Plan, the provisions of the Plan shall control.

16. SEVERABILITY. If all or any part of this Agreement or the Plan is declared by any court or governmental authority to be unlawful or invalid, such unlawfulness or invalidity shall not invalidate any portion of this Agreement or the Plan not declared to be unlawful or invalid. Any Section of this Agreement (or part of such a Section) so declared to be unlawful or invalid shall, if possible, be construed in a manner which will give effect to the terms of such Section or part of a Section to the fullest extent possible while remaining lawful and valid.

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17. CHOICE OF LAW. The interpretation, performance and enforcement of this Agreement will be governed by the law of the state of California without regard to such state's conflicts of laws rules.

18. AMENDMENT. This Agreement may not be modified, amended or terminated except by an instrument in writing, signed by you and by a duly authorized representative of the Company. Notwithstanding the foregoing, this Agreement may be amended solely by the Board by a writing which

specifically states that it is amending this Agreement, so long as a copy of such amendment is delivered to you, and provided that no such amendment adversely affecting your rights hereunder may be made without your written consent. Without limiting the foregoing, the Board reserves the right to change, by written notice to you, the provisions of this Agreement in any way it may deem necessary or advisable to carry out the purpose of the grant as a result of any change in applicable laws or regulations or any future law, regulation, ruling, or judicial decision, provided that any such change shall be applicable only to rights relating to that portion of the Award which is then subject to restrictions as provided herein.

EXHIBIT 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Isis Pharmaceuticals, Inc.;

2. Based on my knowledge, this quarterly report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this quarterly report;

3. Based on my knowledge, the condensed consolidated financial statements, and other financial information included in this quarterly report, fairly present in all material respects the financial condition, condensed consolidated results of operations and condensed consolidated cash flows of the registrant as of, and for, the periods presented in this quarterly report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: August 6, 2012

/s/ Stanley T. Crooke

Stanley T. Crooke, M.D., Ph.D.
Chief Executive Officer

EXHIBIT 31.2

CERTIFICATION

I, B. Lynne Parshall, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Isis Pharmaceuticals, Inc.;

2. Based on my knowledge, this quarterly report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this quarterly report;

3. Based on my knowledge, the condensed consolidated financial statements, and other financial information included in this quarterly report, fairly present in all material respects the financial condition, condensed consolidated results of operations and condensed consolidated cash flows of the registrant as of, and for, the periods presented in this quarterly report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: August 6, 2012

/s/ B. Lynne Parshall

B. Lynne Parshall, J.D.
Chief Financial Officer

Exhibit 32.1

CERTIFICATION

Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, Stanley T. Crooke, the Chief Executive Officer of Isis Pharmaceuticals, Inc., (the "Company"), and B. Lynne Parshall, the Chief Financial Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

1. The Company's Quarterly Report on Form 10-Q for the period ended June 30, 2012, to which this Certification is attached as Exhibit 32.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

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

Dated: August 6, 2012

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

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