UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

Form 10-Q

(Mark One)

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

For the Quarterly Period Ended September 30, 2013

OR

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

For the transition period from to

Commission file number 0-19125

Isis Pharmaceuticals, Inc.

(Exact name of Registrant as specified in its charter)

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

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

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

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

Securities registered pursuant to Section 12(g) of the Act:
Common Stock, $.001 Par Value

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

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

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

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

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

The number of shares of voting common stock outstanding as of November 1, 2013 was 116,074,372.

ISIS PHARMACEUTICALS, INC.
FORM 10-Q
INDEX

TRADEMARKS

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

Regulus Therapeutics™ is a trademark of Regulus Therapeutics Inc.

KYNAMRO™ is a trademark of Genzyme Corporation

Table of Contents

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

	September 30, 2013 (Unaudited)	December 31, 2012
ASSETS		
Current assets:		
Cash and cash equivalents	$ 256,408	$ 124,482
Short-term investments	414,490	249,964
Contracts receivable	12,645	522
Inventories	7,385	6,121
Investment in Regulus Therapeutics Inc.	65,004	33,622
Other current assets	7,372	8,727
Total current assets	763,304	423,438

Property, plant and equipment, net	87,273	91,084
Licenses, net	5,048	6,579
Patents, net	20,810	18,646
Deposits and other assets	5,481	5,939
Total assets	$ 881,916	$ 545,686
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 8,781	$ 10,239
Accrued compensation	6,653	7,878
Accrued liabilities	22,283	15,401
Accrued income taxes	4,935	—
Current portion of long-term obligations	4,649	4,879
Current portion of deferred contract revenue	55,977	35,925
Total current liabilities	103,278	74,322
Long-term deferred contract revenue	151,006	66,656
2 3/4 percent convertible senior notes	148,705	143,990
Long-term obligations, less current portion	6,384	7,402
Long-term financing liability for leased facility	71,097	70,550
Total liabilities	480,470	362,920
Stockholders' equity:		
Common stock, $0.001 par value; 200,000,000 shares authorized, 115,998,221 and 101,481,134 shares issued and outstanding at September 30, 2013 and December 31, 2012, respectively	116	102
Additional paid-in capital	1,315,643	1,077,150
Accumulated other comprehensive income	29,021	12,480
Accumulated deficit	(943,334)	(906,966)
Total stockholders' equity	401,446	182,766
Total liabilities and stockholders' equity	$ 881,916	$ 545,686

See accompanying notes.

Table of Contents

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2013	2012	2013	2012
Revenue:				
Research and development revenue under collaborative agreements	$ 23,383	$ 11,127	$ 102,918	$ 80,085
Licensing and royalty revenue	202	474	2,118	2,091
Total revenue	23,585	11,601	105,036	82,176
Expenses:				
Research, development and patent expenses	45,660	36,551	126,603	115,700
General and administrative	3,430	3,096	10,241	9,281
Total operating expenses	49,090	39,647	136,844	124,981
Loss from operations	(25,505)	(28,046)	(31,808)	(42,805)
Other income (expense):				
Equity in net loss of Regulus Therapeutics Inc.	—	—	—	(1,139)
Investment income	434	408	1,400	1,485
Interest expense	(4,867)	(5,937)	(14,470)	(16,335)
Gain on investments, net	175	—	2,073	19
Loss on early retirement of debt	—	(4,770)	—	(4,770)
Loss before income tax benefit	(29,763)	(38,345)	(42,805)	(63,545)
Income tax benefit	5,193	706	6,437	704
Net loss	$ (24,570)	$ (37,639)	$ (36,368)	$ (62,841)
Basic and diluted net loss per share	$ (0.21)	$ (0.37)	$ (0.33)	$ (0.63)
Shares used in computing basic and diluted net loss per share	115,263	100,680	108,608	100,351

See accompanying notes.

Table of Contents

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2013	2012	2013	2012
Net loss	$ (24,570)	$ (37,639)	$ (36,368)	$ (62,841)
Unrealized gains (losses) on securities, net of tax	2,207	(122)	17,876	1,616
Reclassification adjustment for realized gain included in net loss	(172)	—	(1,335)	—
Comprehensive loss	$ (22,535)	$ (37,761)	$ (19,827)	$ (61,225)

See accompanying notes.

Table of Contents

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

	Nine Months Ended September 30,	
	2013	2012
Net cash provided by (used in) operating activities	$ 77,985	$ (34,159)
Investing activities:		
Purchases of short-term investments	(303,862)	(172,581)
Proceeds from the sale of short-term investments	135,130	189,397
Purchases of property, plant and equipment	(1,113)	(1,033)
Acquisition of licenses and other assets, net	(2,721)	(2,779)
Purchases of strategic investments	—	(40)
Proceeds from sale of strategic investments	2,110	—
Net cash (used in) provided by investing activities	(170,456)	12,964
Financing activities:		
Proceeds from equity awards	56,898	7,789
Proceeds from issuance of 2¾ percent convertible senior notes, net of issuance costs	—	194,689
Principal and premium payment on redemption of the 2⅝ percent convertible subordinated notes	—	(163,718)
Net proceeds from public common stock offering	173,292	—
Proceeds from equipment financing arrangement	2,513	9,100
Principal payments on debt and capital lease obligations	(8,306)	(7,579)
Net cash provided by financing activities	224,397	40,281
Net increase in cash and cash equivalents	131,926	19,086
Cash and cash equivalents at beginning of period	124,482	65,477
Cash and cash equivalents at end of period	$ 256,408	$ 84,563
Supplemental disclosures of cash flow information:		
Interest paid	$ 3,079	$ 5,584
Income taxes paid	$ 2	$ —
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 835	$ 839

See accompanying notes.

Table of Contents

ISIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
September 30, 2013

(Unaudited)

1. Basis of Presentation

The unaudited interim condensed consolidated financial statements for the three and nine month periods ended September 30, 2013 and 2012 have been prepared on the same basis as the audited financial statements for the year ended December 31, 2012. 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, 2012 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. In addition to our wholly owned subsidiary, our condensed consolidated financial statements include our equity investment in Regulus Therapeutics Inc. In October 2012, Regulus completed an initial public offering (IPO). We now own less than 20 percent of Regulus' common stock and we no longer have significant influence over the operating and financial policies of Regulus. As a result, in the fourth quarter of 2012, we stopped using the equity method of accounting for our equity investment in Regulus and we began accounting for our investment at fair value.

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 condensed 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. Delivered items have stand-alone value if they are sold separately by any vendor or the customer could resell the delivered items on a standalone basis. 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 certain deliverables as a single unit of accounting, then we recognize the revenue ratably over our estimated period of performance.

In December 2012, we entered into a collaboration agreement with AstraZeneca to discover and develop antisense therapeutics against five cancer targets. As part of the collaboration, we received a $25 million upfront payment in December 2012 and a $6 million payment in June 2013 when AstraZeneca elected to continue the research collaboration. We are also eligible to receive milestone payments, license fees for the research program targets and royalties on any product sales of drugs resulting from this collaboration. In exchange, we granted AstraZeneca an exclusive license to develop and commercialize ISIS-STAT3$_{Rx}$ and ISIS-AR$_{Rx}$, which we previously referred to as ISIS-AZ1$_{Rx}$. We also granted AstraZeneca options to license up to three cancer drugs under the separate research program. We are responsible for completing an ongoing clinical study of ISIS-STAT3$_{Rx}$ and IND-enabling studies for ISIS-AR$_{Rx}$. AstraZeneca is responsible for all other global development, regulatory and commercialization activities for ISIS-STAT3$_{Rx}$ and ISIS-AR$_{Rx}$. In addition, if AstraZeneca exercises its option for any drugs resulting from the research program, AstraZeneca will assume global development, regulatory and commercialization responsibilities for such drug. Since this agreement has multiple elements, we evaluated the deliverables in this arrangement and determined that certain deliverables, either individually or in combination, have stand-alone value. Below is a list of the four separate units of accounting under our agreement:

Table of Contents

- The exclusive license we granted to AstraZeneca to develop and commercialize ISIS-STAT3$_{Rx}$ for the treatment of cancer;
- The development services we are performing for ISIS-STAT3$_{Rx}$;
- The exclusive license we granted to AstraZeneca to develop and commercialize ISIS-AR$_{Rx}$ and the research services we are performing for ISIS-AR$_{Rx}$; and
- The option to license up to three drugs under a research program and the research services we will perform for this program.

We determined that the ISIS-STAT3$_{Rx}$ license had stand-alone value because it is an exclusive license that gives AstraZeneca the right to develop ISIS-STAT3$_{Rx}$ or to sublicense its rights. In addition, ISIS-STAT3$_{Rx}$ is currently in development and it is possible that AstraZeneca or another third party could conduct clinical trials without assistance from us. As a result, we consider the ISIS-STAT3$_{Rx}$ license and the development services for ISIS-STAT3$_{Rx}$ to be separate units of accounting. We recognized the portion of the consideration allocated to the ISIS-STAT3$_{Rx}$ license immediately because we delivered the license and earned the revenue. We are recognizing the amount allocated to the development services for ISIS-STAT3$_{Rx}$ as revenue over the period of time we perform services. The ISIS-AR$_{Rx}$ license is also an exclusive license. Because of the early stage of research for ISIS-AR$_{Rx}$, we believe that our knowledge and expertise with antisense technology is essential for AstraZeneca or another third party to successfully develop ISIS-AR$_{Rx}$. As a result, we concluded that the ISIS-AR$_{Rx}$ license does not have stand-alone value and we combined the ISIS-AR$_{Rx}$ license and related research services into one unit of accounting. We are recognizing revenue for the combined unit of accounting over the period of time we perform services. We determined that the options under the research program did not have stand-alone value because AstraZeneca cannot develop or commercialize drugs resulting from the research program until AstraZeneca

exercises the respective option or options. As a result, we considered the research options and the related research services as a combined unit of accounting. We are recognizing revenue for the combined unit of accounting over the period of our performance.

We determined that the initial allocable arrangement consideration was the $25 million upfront payment because it was the only payment that was fixed and determinable when we entered into the agreement. In June 2013, we increased the allocable consideration to $31 million when we received the $6 million payment. There was considerable uncertainty at the date of the agreement as to whether we would earn the milestone payments, royalty payments, payments for manufacturing clinical trial materials or payments for finished drug product. As such, we did not include those payments in the allocable consideration.

We allocated the allocable consideration based on the relative BESP of each unit of accounting. We engaged a third party, independent valuation expert to assist us with determining BESP. We estimated the selling price of the licenses granted for ISIS-STAT3$_{Rx}$ and ISIS-AR$_{Rx}$ by using the relief from royalty method. Under this method, we estimated the amount of income, net of taxes, for each drug. We then discounted the projected income for each license to present value. The significant inputs we used to determine the projected income of the licenses included:

- Estimated future product sales;
- Estimated royalties on future product sales;
- Contractual milestone payments;
- Expenses we expect to incur;
- Income taxes; and
- An appropriate discount rate.

We estimated the selling price of the research and development services by using our internal estimates of the cost to perform the specific services, marked up to include a reasonable profit margin, and estimates of expected cash outflows to third parties for services and supplies over the expected period that we will perform research and development. The significant inputs we used to determine the selling price of the research and development services included:

- The number of internal hours we will spend performing these services;
- The estimated number and cost of studies we will perform;
- The estimated number and cost of studies that we will contract with third parties to perform; and
- The estimated cost of drug product we will use in the studies.

As a result of the allocation, we recognized $9.3 million of the $25 million upfront payment for the ISIS-STAT3$_{Rx}$ license in December 2012 and we recognized $2.2 million of the $6 million payment for the ISIS-STAT3$_{Rx}$ license in June 2013. We are recognizing the remaining $19.5 million of the $31 million over the estimated period of our performance. Assuming a constant selling price for the other elements in the arrangement, if there was an assumed ten percent increase or decrease in the estimated selling price of the ISIS-STAT3$_{Rx}$ license, we determined that the revenue we would have allocated to the ISIS-STAT3$_{Rx}$ license would change by approximately seven percent, or $750,000, from the amount we recorded.

Table of Contents

Typically, 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.

From time to time, we may enter into separate agreements at or near the same time with the same customer. We evaluate such agreements to determine whether they should be accounted for individually as distinct arrangements or whether the separate agreements are, in substance, a single multiple element arrangement. We evaluate whether the negotiations are conducted jointly as part of a single negotiation, whether the deliverables are interrelated or interdependent, whether fees in one arrangement are tied to performance in another arrangement, and whether elements in one arrangement are essential to another arrangement. Our evaluation involves significant judgment to determine whether a group of agreements might be so closely related that they are, in effect, part of a single arrangement. For example, since early 2012 we have entered into four collaboration agreements with Biogen Idec:

- 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 clinical trials.

- In June 2012, we entered into a second and 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 a Phase 2 clinical trial.

- In December 2012, we entered into a third and separate collaboration agreement with Biogen Idec to discover and develop antisense drugs against three targets to treat neurological or neuromuscular disorders. As part of the collaboration, we received a $30 million upfront payment and we are responsible for the discovery of a lead antisense drug for each of three targets.

- In September 2013, we entered into a fourth and separate collaboration agreement with Biogen Idec to leverage antisense technology to advance the treatment of neurological diseases. We granted Biogen Idec exclusive rights to the use of our antisense technology to develop therapies for neurological diseases as part of this broad collaboration. We received a $100 million upfront payment and we are responsible for discovery and early development through the completion of a Phase 2 clinical trial for each antisense drug developed under this collaboration, while Biogen Idec is responsible for the creation and development of small molecule treatments and biologics.

All four of these collaboration agreements give Biogen Idec the option or options to license one or more drugs resulting from the specific collaboration. If Biogen Idec exercises an option, it will pay us a license fee and will assume future development, regulatory and commercialization

responsibilities for the licensed drug. We are also eligible to receive milestone payments associated with the research and/or development of the drugs prior to licensing, milestone payments if Biogen Idec achieves pre-specified regulatory milestones, and royalties on any product sales of drugs resulting from these collaborations.

We evaluated all four of the Biogen Idec agreements to determine whether we should account for them as separate agreements. We determined that we should account for the agreements separately because we conducted the negotiations independently of one another, each agreement focuses on different drugs, there are no interrelated or interdependent variables, there are no provisions in any of these agreements that are essential to the other agreement, and the payment terms and fees under each agreement are independent of each other. We also evaluated the deliverables in each of these agreements to determine whether they met 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. For all four of these agreements, we determined that the options did not have stand-alone value because Biogen Idec cannot pursue the development or commercialization of the drugs resulting from these collaborations until it exercises the respective option or options. As such, for each agreement we considered the deliverables to be a single unit of accounting and we are recognizing the upfront payment for each of the agreements over the respective 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.

Table of Contents

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 that 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.

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

Table of Contents

technologies we discover, we have determined that all future development, regulatory and commercialization milestones are substantive. For example, for our strategic alliance with Biogen Idec, we are using our antisense drug discovery platform to seek out and develop new drugs against targets for neurological diseases. Alternatively, we provide on-going access to our technology to Alnylam Pharmaceuticals, Inc. to develop and commercialize RNA interference, or RNAi, therapeutics. We consider milestones for both of these collaborations 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 do not consider the milestone to be substantive and we defer recognition of the milestone payment and recognize it as revenue over the estimated period of performance, if any. We earned $60.5 million in milestone payments in the first nine months of 2013, including a $25 million milestone payment from Genzyme we recognized in the first quarter of 2013 when the FDA approved the KYNAMRO NDA. We consider milestone payments 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 $60.5 million in milestone payments in the first nine months of 2013. Further information about our collaborative arrangements can be found in Note 8, *Collaborative Arrangements and Licensing Agreements*, below and Note 7, *Collaborative Arrangements and Licensing Agreements*, of our audited financial statements for the year ended December 31, 2012 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.

Research, development and patent expense

We expense research and development costs as we incur them. We include wages, benefits, facilities, supplies, external services, clinical trial and manufacturing costs, and other expenses that are directly related to our research and development operations in research and development expense. For the three and nine months ended September 30, 2013, research and development expenses were $45.0 million and $122.8 million, respectively, compared to $35.6 million and $113.4 million for the same periods in 2012.

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. We include non-cash charges for amortization and write-downs of capitalized patent costs, as well as legal fees for patent litigation and patent defense in patent expense. For the three and nine months ended September 30, 2013, patent expenses were $695,000 and $3.8 million, respectively, compared to $988,000 and $2.3 million for the same periods in 2012. Patent expenses include non-cash charges related to the write-down of our patent costs to their estimated net realizable values of $166,000 and $441,000 for the three and nine months ended September 30, 2013, respectively, compared to $376,000 and $664,000 for the same periods in 2012.

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 comprehensive income (loss) and include net realized gains and losses in gain (loss) on investments. We use the specific identification method to determine the cost of securities sold.

We have equity investments in privately- and publicly-held biotechnology companies that we have received as part of a technology license or collaboration agreement. At September 30, 2013 we held ownership interests of less than 20 percent in each of the respective companies.

Table of Contents

We account for our equity investments in publicly-held companies at fair value and record unrealized gains and losses related to temporary increases and decreases in the stock of these publicly-held companies as a separate component of comprehensive income (loss). We account for equity investments in privately-held companies under the cost method of accounting because we own less than 20 percent and do not have significant influence over their operations. 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. 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. 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 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 nine months of 2013 and 2012. Total inventory, which consisted of raw materials, was $7.4 million and $6.1 million as of September 30, 2013 and December 31, 2012, respectively.

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 accounted for our ownership interest in Regulus using the equity method of accounting until Regulus' IPO in October 2012. In the fourth quarter of 2012, we began accounting for our investment at fair value because we now own less than 20 percent of Regulus' common stock and we no longer have significant influence over the operating and financial policies of Regulus. Under the equity method of accounting, we included 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."

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 nine months ended September 30, 2013 and 2012, we did not include dilutive common equivalent shares in the computation of diluted net loss per share because the effect would have been anti-dilutive. The following would have had an anti-dilutive effect on net loss per share:

- $2^{3}/_{4}$ percent convertible senior notes;
- $2^{5}/_{8}$ percent convertible subordinated notes;
- GlaxoSmithKline convertible promissory notes issued by Regulus;
- Dilutive stock options; and
- Unvested restricted stock units.

Table of Contents

We redeemed all of our $2^{5}/_{8}$ percent notes in September 2012 and in October 2012 Regulus completed an IPO, upon which we were no longer guarantors on the two convertible notes that Regulus issued to GSK. As a result, the $2^{5}/_{8}$ percent notes and GSK convertible promissory notes are not common equivalent shares for the three and nine months ended September 30, 2013.

Public Common Stock Offering

In June 2013, we completed the sale of 9,617,869 shares of our common stock through a public offering at a price of $19.00 per share, which included 617,869 additional shares sold pursuant to an option we granted to the underwriters. We received net proceeds of approximately $173.2 million from the sale of these shares net of underwriting discounts and commissions and other estimated offering expenses of $9.5 million.

Consolidation of variable interest entities

We identify entities as variable interest entities either: (1) that do not have sufficient equity investment at risk to permit the entity to finance its activities without additional subordinated financial support, or (2) in which the equity investors lack an essential characteristic of a controlling financial interest. We perform ongoing qualitative assessments of our variable interest entities to determine whether we have a controlling financial interest in the variable interest entity and therefore are the primary beneficiary. As of September 30, 2013 and December 31, 2012, we had collaborative arrangements with five and six entities, respectively, 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. As of September 30, 2013, the total carrying value of our investments in variable interest entities was $66.8 million, and was primarily related to our investment in Regulus. Our maximum exposure to loss related to these variable interest entities is limited to the carrying value of our investments.

Accumulated other comprehensive income

Accumulated other comprehensive income is comprised of unrealized gains and losses on securities, net of taxes, and adjustments we made to reclassify realized gains and losses on securities from other accumulated comprehensive income to our condensed consolidated statement of operations. The

following table summarizes changes in accumulated other comprehensive income for the three and nine months ended September 30, 2013 and 2012 (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2013	2012	2013	2012
Beginning balance accumulated other comprehensive income (loss)	$ 26,986	$ 968	$ 12,480	$ (770)
Other comprehensive income (loss) before reclassifications, net of tax (1)	2,207	(122)	17,876	1,616
Amounts reclassified from accumulated other comprehensive income (2)	(172)	—	(1,335)	—
Net current period other comprehensive income (loss)	2,035	(122)	16,541	1,616
Ending balance accumulated other comprehensive income	$ 29,021	$ 846	$ 29,021	$ 846

(1) Other comprehensive income includes income tax expense of $1.4 million and $11.4 million, respectively, for the three and nine months ended September 30, 2013 and $1.1 million for the three and nine months ended September 30, 2012.

(2) Included in gain on investments, net on our condensed consolidated statement of operations.

Table of Contents

Convertible debt

In August 2012, we completed a $201.3 million offering of convertible senior notes, which mature in 2019 and bear interest at 2¾ percent. In September 2012, we used a substantial portion of the net proceeds from the issuance of the 2¾ percent notes to redeem our 2⁵¤₈ percent convertible subordinated notes. Consistent with how we accounted for our 2⁵¤₈ percent notes, we account for our 2¾ percent notes by separating the liability and equity components of the instrument in a manner that reflects our nonconvertible debt borrowing rate. As a result, we assigned a value to the debt component of our 2¾ percent notes equal to the estimated fair value of similar debt instruments without the conversion feature, which resulted in us recording the debt instrument at a discount. We are amortizing the debt discount over the life of these 2¾ percent notes 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 our Employee Stock Purchase Plan, or ESPP, based on the estimated fair value of the award on the date of grant using an option-pricing model. We recognize the value of the portion of the award that we ultimately expect to vest as stock-based compensation expense over the requisite service period in our condensed consolidated statements of operations. We reduce stock-based compensation expense for estimated forfeitures at the time of grant and revise in subsequent periods if actual forfeitures differ from those estimates.

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 estimate the expected term of options granted based on historical exercise patterns. For the nine months ended September 30, 2013 and 2012, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Nine Months Ended September 30,	
	2013	2012
Risk-free interest rate	1.0%	1.0%
Dividend yield	0.0%	0.0%
Volatility	51.4%	50.7%
Expected life	5.1 years	5.1 years

ESPP:

	Nine Months Ended September 30,	
	2013	2012
Risk-free interest rate	0.1%	0.2%
Dividend yield	0.0%	0.0%
Volatility	62.9%	49.6%
Expected life	6 months	6 months

Board of Director Stock Options:

	Nine Months Ended September 30,	
	2013	2012
Risk-free interest rate	2.2%	1.3%
Dividend yield	0.0%	0.0%
Volatility	52.7%	51.3%
Expected life	7.2 years	7.6 years

The fair value of RSUs is based on the market price of our common stock on the date of grant. RSUs vest annually over a four year period. The weighted-average grant date fair value of RSUs granted to employees and the Board of Directors for the nine months ended September 30, 2013 was $15.29 and $27.95, respectively. The weighted-average grant date fair value of RSUs granted to employees and the Board of Directors for the nine months ended September 30, 2012 was $7.97 and $12.94, respectively.

The following table summarizes stock-based compensation expense for the three and nine months ended September 30, 2013 and 2012 (in thousands), which was allocated as follows:

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2013	2012	2013	2012
Research and development	$ 2,373	$ 1,720	$ 7,171	$ 5,728
General and administrative	439	314	1,147	1,033
Total	$ 2,812	$ 2,034	$ 8,318	$ 6,761

As of September 30, 2013, total unrecognized estimated non-cash stock-based compensation expense related to non-vested stock options and RSUs was $10.1 million and $3.3 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 1.2 years and 1.7 years, respectively.

Impact of recently issued accounting standards

In February 2013, the FASB issued guidance requiring enhanced disclosures related to reclassifications out of accumulated other comprehensive income (loss). Under the guidance, we must disclose the amounts we reclassified out of accumulated other comprehensive income (loss) by component. In addition, for significant amounts that we reclassified entirely from other comprehensive income (loss) to net loss, we must disclose the line item of net loss, either on the face of the statement of operations or in the notes to the financial statements. For amounts that we did not reclassify entirely to net loss, we must cross-reference to other disclosures that provide additional detail about those amounts. The guidance is effective retrospectively for fiscal years, and interim periods within those years, beginning after December 15, 2012 and was effective for our fiscal year beginning January 1, 2013. As this guidance relates to disclosure only, the adoption of this guidance did not have any effect on our financial statements.

3. Investments

As of September 30, 2013, we have primarily invested our excess cash in 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 September 30, 2013:

One year or less	39%
After one year but within two years	42%
After two years but within three years	19%
Total	100%

As illustrated above, we primarily invest our excess cash in short-term instruments with 81 percent of our available-for-sale securities having a maturity of less than two years.

At September 30, 2013, we had an ownership interest of less than 20 percent in each of three private companies and three public companies with which we conduct business. The privately-held companies are Santaris Pharma A/S (formerly Pantheco A/S), Achaogen Inc., and Atlantic Pharmaceuticals Limited. The publicly-traded companies are Antisense Therapeutics Limited, iCo Therapeutics Inc., and Regulus. We account for equity investments in the privately-held companies under the cost method of accounting and we account for equity investments in the publicly-traded companies at fair value. We record unrealized gains and losses as a separate component of comprehensive income (loss) and include net realized gains and losses in gain (loss) on investments. In the first quarter of 2013, we sold all of the common stock of Sarepta Therapeutics, Inc. that we owned resulting in a realized gain of $1.1 million.

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

	Amortized	Unrealized		Other-Than-Temporary Impairment	Estimated

September 30, 2013	Cost	Gains	Losses	Loss	Fair Value
Available-for-sale securities:					
Corporate debt securities (1)	$ 119,472	$ 65	$ (44)	$ —	$ 119,493
Debt securities issued by U.S. government agencies (1)	19,341	11	(27)	—	19,325
Debt securities issued by the U.S. Treasury	7,257	10	—	—	7,267
Debt securities issued by states of the United States and political subdivisions of the states	16,110	19	(16)	—	16,113
Total securities with a maturity of one year or less	162,180	105	(87)	—	162,198
Corporate debt securities	220,494	87	(507)	—	220,074
Debt securities issued by U.S. government agencies	17,479	22	(6)	—	17,495
Debt securities issued by the U.S. Treasury	9,075	22	—	—	9,097
Debt securities issued by states of the United States and political subdivisions of the states	7,202	25	(1)	—	7,226
Total securities with a maturity of more than one year	254,250	156	(514)	—	253,892
Total	$ 416,430	$ 261	$ (601)	$ —	$ 416,090

September 30, 2013	Cost Basis	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Equity securities:					
Regulus Therapeutics Inc.	$ 15,526	$ 49,478	$ —	$ —	$ 65,004
Securities included in other current assets	1,538	1,174	—	(880)	1,832
Securities included in deposits and other assets	625	—	—	—	625
Total	$ 17,689	$ 50,652	$ —	$ (880)	$ 67,461

Table of Contents

December 31, 2012	Amortized Cost	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Available-for-sale securities:					
Corporate debt securities (1)	$ 115,249	$ 81	$ (9)	$ —	$ 115,321
Debt securities issued by U.S. government agencies (1)	12,100	2	(66)	—	12,036
Debt securities issued by the U.S. Treasury	1,000	1	—	—	1,001
Debt securities issued by states of the United States and political subdivisions of the states	16,560	18	(2)	—	16,576
Total securities with a maturity of one year or less	144,909	102	(77)	—	144,934
Corporate debt securities	80,166	112	(92)	—	80,186
Debt securities issued by U.S. government agencies	8,034	38	—	—	8,072
Debt securities issued by the U.S. Treasury	12,424	27	—	—	12,451
Debt securities issued by states of the United States and political subdivisions of the states	8,306	31	(16)	—	8,321
Total securities with a maturity of more than one year	108,930	208	(108)	—	109,030
Total	$ 253,839	$ 310	$ (185)	$ —	$ 253,964

December 31, 2012	Cost Basis	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Equity securities:					
Regulus Therapeutics Inc.	$ 15,526	$ 18,096	$ —	$ —	$ 33,622
Securities included in other current assets	1,579	4,175	—	(880)	4,874
Securities included in deposits and other assets	625	—	—	—	625
Total	$ 17,730	$ 22,271	$ —	$ (880)	$ 39,121

(1) Includes investments classified as cash equivalents on our condensed consolidated balance sheet.

We believe that the decline in value of certain of our 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.

Investments we considered to be temporarily impaired at September 30, 2013 were as follows (in thousands):

		Less than 12 months of temporary impairment	
	Number of Investments	Estimated Fair Value	Unrealized Losses
Corporate debt securities	137	$ 218,610	$ (551)
Debt securities issued by U.S. government agencies	4	19,976	(33)
Debt securities issued by states of the United States and political subdivisions of the states	4	5,104	(17)
Total temporarily impaired securities	145	$ 243,690	$ (601)

Table of Contents

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 an investment in equity securities in a publicly-held biotechnology company; 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. Our Level 3 investments include investments in the equity securities of publicly-held biotechnology companies for which we calculated a lack of marketability discount because there are restrictions on when we can trade the securities. The majority of our securities have been classified as Level 2. We obtain the fair value of our Level 2 investments from our custodian banks or from a professional pricing service. We validate the fair value of our Level 2 investments by understanding the pricing model used by the custodian bank or professional pricing service provider and comparing that fair value to the fair value based on observable market prices. During the three and nine months ended September 30, 2013 and 2012 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.

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 September 30, 2013 and December 31, 2012 as follows (in thousands):

	At September 30, 2013	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 241,007	$ 239,407	$ 1,600	$ —
Corporate debt securities (2)	337,967	—	337,967	—
Debt securities issued by U.S. government agencies (2)	36,820	—	36,820	—
Debt securities issued by the U.S. Treasury (2)	16,364	16,364	—	—
Debt securities issued by states of the United States and political subdivisions of the states (2)	23,339	—	23,339	—
Investment in Regulus Therapeutics Inc.	65,004	—	—	65,004
Equity securities (3)	1,832	1,832	—	—
Total	$ 722,333	$ 257,603	$ 399,726	$ 65,004

	At December 31, 2012	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 105,496	$ 101,496	$ 4,000	$ —
Corporate debt securities (2)	193,507	—	193,507	—
Debt securities issued by U.S. government agencies (2)	18,108	—	18,108	—
Debt securities issued by the U.S. Treasury (2)	13,452	13,452	—	—
Debt securities issued by states of the United States and political subdivisions of the states (2)	24,897	—	24,897	—
Investment in Regulus Therapeutics Inc.	33,622	—	—	33,622
Equity securities (3)	4,874	4,146	—	728
Total	$ 393,956	$ 119,094	$ 240,512	$ 34,350

(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.

We classified the fair value measurements of our investments in the equity securities of Regulus and Sarepta Therapeutics, Inc., or Sarepta, as Level 3. We calculated a lack of marketability discount on the fair value of these investments because of trading restrictions on the securities. We consider the inputs we used to calculate the lack of marketability discount Level 3 inputs and, as a result, we categorized these investments as Level 3. We determined the lack of marketability discount by using a Black-Scholes model to value a hypothetical put option to approximate the cost of hedging the stock until the restriction ends. In the first quarter of 2013, we sold all of the common stock of Sarepta that we owned resulting in a realized gain of $1.1 million. As of

Table of Contents

September 30, 2013, our Level 3 investments consisted of our investment in Regulus, with a gross fair value of $66.5 million less a lack of marketability discount of $1.5 million for a net carrying value of $65.0 million. As of December 31, 2012, our Level 3 investments consisted of our investment in Regulus and Sarepta with a gross fair value of $44.4 million and $1.0 million, respectively, less a lack of marketability discount of $10.8 million and $296,000, respectively, for a net carrying value of $33.6 million and $728,000, respectively.

The following is a summary of our investments measured at fair value on a recurring basis using significant unobservable inputs (Level 3) for the nine months ended September 30, 2013 and 2012 (in thousands):

	Nine Months Ended September 30,

	2013	2012
Beginning balance of Level 3 investments	$ 34,350	$ —
Purchases	—	40
Total gains and losses:		
Included in gain on investments	(1,163)	—
Included in accumulated other comprehensive income	33,329	337
Cost basis of shares sold	(40)	—
Ending balance of Level 3 investments	$ 66,476	$ 377

Other Fair Value Disclosures

Our 2¾ percent convertible senior notes had a fair value of $480.6 million at September 30, 2013. We determine the fair value of our 2¾ percent convertible senior 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 an equipment financing loan agreement 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 and in June 2013 we drew down $2.5 million in principal at an interest rate of 4.38 percent. As of September 30, 2013, our outstanding borrowings under this loan agreement were at a weighted average interest rate of 4.34 percent and we can borrow up to an additional $3.4 million in principal to finance the purchase of equipment until April 2014. The carrying balance under this loan agreement at September 30, 2013 and December 31, 2012 was $8.7 million and $10.0 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 September 30,		Nine Months Ended September 30,	
	2013	2012	2013	2012
Partner A	48%	18%	22%	7%
Partner B	18%	0%	21%	0%
Partner C	25%	21%	16%	7%
Partner D	0%	41%	31%	78%

Contract receivables from two significant partners comprised approximately 93 percent of our contract receivables at September 30, 2013. Contract receivables from four significant partners comprised approximately 83 percent of our contract receivables at December 31, 2012.

Table of Contents

7. Income Taxes

Intraperiod tax allocation rules require us to allocate our provision for income taxes between continuing operations and other categories of earnings, such as other comprehensive income. In periods in which we have a year-to-date pre-tax loss from continuing operations and pre-tax income in other categories of earnings, such as other comprehensive income, we must allocate the tax provision to the other categories of earnings. We then record a related tax benefit in continuing operations. During the first nine months of 2013, we recorded unrealized gains on our investments in available-for-sale securities in other comprehensive income net of taxes. As a result, we recorded a $6.4 million tax benefit on our condensed consolidated statements of operations and an $11.4 million tax expense in other comprehensive income for the nine months ended September 30, 2013.

8. Collaborative Arrangements and Licensing Agreements

Traditional Pharmaceutical Alliances and Licensing

AstraZeneca

In December 2012, we entered into a global collaboration agreement with AstraZeneca to discover and develop antisense drugs against five cancer targets. The agreement includes $31 million in upfront and near-term payments comprised of a $25 million upfront payment we received in December 2012 and a $6 million payment we received in June 2013 when AstraZeneca elected to continue the research collaboration. We are also eligible to receive milestone payments, license fees and double-digit royalties on any product sales of drugs resulting from this collaboration. As part of the agreement, we granted AstraZeneca an exclusive license to develop and commercialize ISIS-STAT3$_{Rx}$ and ISIS-AR$_{Rx}$, which we previously referred to as ISIS-AZ1$_{Rx}$, for the treatment of cancer and an option to license up to three cancer drugs under a separate research program.

Together with AstraZeneca, we are evaluating ISIS-STAT3$_{Rx}$ in patients with advanced cancer. AstraZeneca is conducting a Phase 1b/2a clinical study of ISIS-STAT3$_{Rx}$ in patients with advanced metastatic hepatocellular carcinoma, or HCC. We are concurrently completing a clinical study evaluating ISIS-STAT3$_{Rx}$ in patients with advanced lymphomas, including patients with diffuse large b-cell lymphoma. We are responsible for completing our clinical study in patients with advanced lymphomas and AstraZeneca is responsible for all other development activities for ISIS-STAT3$_{Rx}$. In June 2013, we earned a $10 million milestone payment when AstraZeneca added a second development candidate, ISIS-AR$_{Rx}$, to our collaboration. ISIS-AR$_{Rx}$ is an antisense drug

designed to treat patients with prostate cancer by inhibiting the production of the androgen receptor, or AR. If AstraZeneca successfully develops drugs under all three cancer programs, we could receive substantive milestone payments of more than $970 million, including up to $315.5 million for the achievement of development milestones and up to $655 million for the achievement of regulatory milestones. We could earn the next milestone payment of up to $50 million if we meet pre-agreed efficacy and safety criteria in our ongoing ISIS-STAT3$_{Rx}$ study in patients with advanced cancer.

In August 2013, we added another collaboration program with AstraZeneca to discover and develop an antisense drug against an undisclosed target. AstraZeneca has the option to license a drug resulting from this research collaboration, and if AstraZeneca exercises its option, it will be responsible for all further development and commercialization of the drug. We received a $750,000 upfront payment and are eligible to receive license fees and substantive milestone payments of nearly $153.2 million, including up to $35.2 million for the achievement of development milestones and up to $105 million for regulatory milestones. We will earn the next $3.2 million milestone payment if a development candidate is identified under this collaboration. In addition, we are eligible to receive up to double-digit royalties on sales from any product that AstraZeneca successfully commercializes under this collaboration.

During the three and nine months ended September 30, 2013, we earned revenue of $4.2 million and $22.0 million, respectively, from our relationship with AstraZeneca, which represented 18 percent and 21 percent, respectively, of our total revenue for those periods. Our balance sheets at September 30, 2013 and December 31, 2012 included deferred revenue of $14.3 million and $15.7 million, respectively, related to our relationship with AstraZeneca.

Biogen Idec

We have established four strategic collaborations with Biogen Idec that broaden and expand our severe and rare disease franchise. In January 2012, we entered into a global collaboration agreement with Biogen Idec to develop and commercialize ISIS-SMN$_{Rx}$ for the treatment of SMA. Biogen Idec has the option to license ISIS-SMN$_{Rx}$ until completion of the first successful Phase 2/3 study or the completion of two Phase 2/3 studies. If Biogen Idec exercises its option, it will pay us a license fee and will assume global development, regulatory and commercialization responsibilities. In April 2013, we initiated a Phase 2 study of ISIS-SMN$_{Rx}$ in infants with SMA, which began the Phase 2/3 program for ISIS-SMN$_{Rx}$. Under the terms of the agreement, we received an upfront payment of $29 million and over the term of the collaboration are eligible to receive up to $270 million in a license fee and substantive milestone payments. We are eligible to receive $45 million in milestone payments associated with the clinical development of ISIS-SMN$_{Rx}$ prior to licensing, of which we have earned $5.5 million in milestone payments for advancing the Phase 2 study of ISIS-SMN$_{Rx}$ in infants with SMA.

To date, we have earned two of the four payments under the March 2013 amendment to the payment terms for the $18 million milestone payment we could earn for the progression of this Phase 2/3 study in infants. We will earn a $1.5 million milestone payment, the third of four payments, if we dose the eighth patient in a Phase 3 study of ISIS-SMN$_{Rx}$ in infants. We are also eligible to receive up to $150 million in milestone payments if Biogen Idec achieves pre-specified regulatory milestones. In addition, we are eligible to receive up to double-digit royalties on any product sales of ISIS-SMN$_{Rx}$.

In June 2012, we and Biogen Idec entered into a second and separate collaboration and license agreement to develop and commercialize a novel antisense drug targeting DMPK for the treatment of myotonic dystrophy type 1, or DM1. We are responsible for global development of the drug through the completion of a Phase 2 clinical trial. Biogen Idec has the option to license the drug through the completion of the Phase 2 trial. Under the terms of the agreement, we received an upfront payment of $12 million and over the term of the collaboration are eligible to receive up to $259 million in a license fee and substantive milestone payments. In October 2013, we earned a $10 million milestone payment when we initiated an IND-enabling toxicology study on a drug targeting DMPK, ISIS-DMPK$_{Rx}$, and we are eligible to receive up to another $49 million in milestone payments associated with the development of ISIS-DMPK$_{Rx}$ prior to licensing. We are also eligible to receive up to $130 million in milestone payments if Biogen Idec achieves pre-specified regulatory milestones. In addition, we are eligible to receive up to double-digit royalties on any product sales of the drug. We will earn the next milestone payment of $14 million if we initiate a Phase 1 study for ISIS-DMPK$_{Rx}$.

In December 2012, we and Biogen Idec entered into a third and separate collaboration to develop and commercialize novel antisense drugs to three targets to treat neurological or neuromuscular diseases. We are responsible for the development of the drugs through the completion of the initial Phase 2 clinical study. Biogen Idec has the option to license a drug from each of the three programs through the completion of Phase 2 studies. Under the terms of the agreement, we received an upfront payment of $30 million and over the term of the collaboration are eligible to receive up to $259 million in a license fee and substantive milestone payments per program. We could receive up to $59 million in development milestone payments to support research and development of each program, including amounts related to the cost of clinical trials, and up to $130 million in milestone payments if Biogen Idec achieves pre-specified regulatory milestones. In addition, we are eligible to receive double-digit royalties on any product sales of drugs resulting from each of the three programs. We will earn the next milestone payment of $10 million if we initiate an IND-enabling toxicology study for a development candidate identified under this collaboration.

In September 2013, we and Biogen Idec entered into a fourth and separate collaboration, which is a long-term strategic relationship focused on applying antisense technology to advance the treatment of neurological diseases. As part of the collaboration, Biogen Idec will gain exclusive rights to the use of our antisense technology to develop therapies for neurological diseases and has the option to license drugs resulting from this collaboration. The exclusivity for neurological diseases will last six years, and may be extended for the specific drug development programs being pursued under the collaboration. Under the terms of the agreement, we received an upfront payment of $100 million and are eligible to receive milestone payments, license fees and royalty payments for all drugs developed through this collaboration, with the specific amounts dependent upon the modality of the molecule advanced by Biogen Idec. If we have a change of control during the first six years of the collaboration, we may be required to refund Biogen Idec a portion of the $100 million upfront payment, with the amount of the potential refund decreasing ratably as we progress through the initial six year term of the collaboration. We recorded the $100 million upfront payment as deferred revenue and will begin amortizing it over our period of performance in October 2013. Because the amortization period for the upfront payment will never be less than the initial six year term of the collaboration, the amount of revenue we recognize from the upfront payment will never exceed the amount that Biogen Idec could potentially require us to refund.

If an antisense molecule is chosen for drug discovery and development of a neurological disease, we are eligible to receive up to approximately $260 million in a license fee and substantive milestone payments for each antisense drug developed under the collaboration. We are eligible to receive up to approximately $60 million for the achievement of development milestones, including amounts related to the cost of clinical trials, and up to $130 million for the achievement of regulatory milestones. We will usually be responsible for drug discovery and early development of antisense drugs and Biogen Idec will have the option to license antisense drugs after Phase 2 proof of concept. Biogen Idec will then be responsible for later phase development and commercialization of the licensed drug. In addition, we are eligible to receive double-digit royalties on any product sales of antisense drugs developed under

this collaboration. If other modalities, such as small molecules or monoclonal antibodies are chosen, we have the opportunity to receive up to $90 million in substantive milestone payments, including up to $35 million for the achievement of development milestones and up to $55 million for the achievement of regulatory milestones. Biogen Idec will be responsible for all of the drug discovery and development activities for drugs using other modalities. In addition, we are eligible to receive single-digit royalties on any product sales of any drugs using other modalities developed under this collaboration. We could earn the next milestone payment of up to $10 million if we choose a target to advance under this collaboration.

During the three and nine months ended September 30, 2013, we earned revenue of $5.9 million and $17.1 million, respectively, from our relationships with Biogen Idec, which represented 25 percent and 16 percent, respectively, of our total revenue for those periods. In comparison, we earned revenue of $2.4 million and $6.0 million for the same periods in 2012. Our balance sheets at September 30, 2013 and December 31, 2012 included deferred revenue of $152.5 million and $62.6 million, respectively, related to the upfront payments.

Table of Contents

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. 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 apo-B by binding to the messenger RNA, or mRNA, encoding apo-B, throughout the world.

The transaction 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 January 2013 we earned a $25 million milestone payment when the FDA approved 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 $700 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 upon the earlier of an NDA approval for the use of KYNAMRO to treat patients who have heterozygous FH or annual net revenue equal to or greater than $250 million in a calendar year.

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 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. In 2011, we satisfied our development funding obligation. As such, we and Genzyme are sharing development expenses equally until KYNAMRO is profitable.

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 nine months ended September 30, 2013, we earned revenue of $32.5 million from our relationship with Genzyme, which represented 31 percent of our total revenue for this period. In comparison, we earned revenue of $4.7 million and $63.9 million for the same periods in 2012. Our balance sheet at December 31, 2012 included deferred revenue of $3.8 million for KYNAMRO drug substance that we shipped to Genzyme in 2013.

Table of Contents

GlaxoSmithKline

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

In October 2012, we and GSK amended the original agreement to reflect an accelerated clinical development plan for ISIS-TTR$_{Rx}$. Under the amended terms of the agreement, we received a $2.5 million upfront payment in December 2012, and we received a $7.5 million milestone payment in February 2013 when we initiated the Phase 2/3 clinical study for ISIS-TTR$_{Rx}$. Most recently, we earned a $2 million milestone payment in July 2013 for advancing the ongoing Phase 2/3 study of ISIS-TTR$_{Rx}$. We have earned $19.5 million in milestone payments from GSK related to the development of ISIS-TTR$_{Rx}$ and we are eligible to earn an additional $48 million in pre-licensing milestone payments associated with the ISIS-TTR$_{Rx}$ Phase 2/3 study. In addition, GSK has increased the regulatory and commercial milestone payments we can earn should ISIS-TTR$_{Rx}$ receive marketing approval and meet certain sales thresholds.

Our strategic alliance currently includes five active programs including the ISIS-TTR$_{Rx}$ program. We are eligible to receive on average up to $20 million in milestone payments up to Phase 2 proof-of-concept for each program, except the ISIS-TTR$_{Rx}$ program, which we describe above. GSK has the option to license drugs from these programs at Phase 2 proof-of-concept, and if GSK exercises its option to a program it will be responsible for all further development and commercialization of the program. In September 2013, we designated ISIS-GSK3$_{Rx}$ as an additional development candidate to our collaboration with GSK. ISIS-GSK3$_{Rx}$ is an antisense drug designed to inhibit the production of an undisclosed target to treat a common viral infection. In September 2013, we earned $7 million in milestone payments associated with advancing the ISIS-GSK3$_{Rx}$ program. Under the terms of the amended agreement, if GSK successfully develops all five programs for one or more indications and achieves pre-agreed sales targets, we could receive license fees and substantive milestone payments of nearly $1.2 billion, including up to $195.5 million for the achievement of development milestones, up to $526.5 million for the achievement of regulatory milestones and up to $445 million for the achievement of commercialization milestones. We will earn the next $2 million milestone payment if we further progress the Phase 2/3 clinical study for ISIS-TTR$_{Rx}$. In addition, we are eligible to receive up to double-digit royalties on sales from any product that GSK successfully commercializes under this alliance.

During the three and nine months ended September 30, 2013, we earned revenue of $11.3 million and $23.5 million, respectively, from our relationship with GSK, which represented 48 percent and 22 percent, respectively, of our total revenue for those periods. In comparison, we earned revenue of $2.1 million and $6.0 million for the same periods in 2012. Our balance sheets at September 30, 2013 and December 31, 2012 included deferred revenue of $13.2 million and $19.9 million, respectively, related to our relationship with GSK.

Roche

In April 2013, we formed an alliance with Hoffman-La Roche Inc. and F. Hoffmann-La Roche Ltd., collectively Roche, to develop treatments for Huntington's disease, or HD, based on our antisense technology. Roche has the option to license the drugs from us through the completion of the first Phase 1 trial. Prior to option exercise, we are responsible for the discovery and development of an antisense drug targeting huntingtin, or HTT, protein. We will also work collaboratively with Roche on the discovery of an antisense drug utilizing Roche's "brain shuttle" program. If Roche exercises its option, it will be responsible for global development, regulatory and commercialization activities for all drugs arising out of the collaboration. Under the terms of the agreement, we received an upfront payment of $30.0 million in April 2013 and we are eligible to receive up to $362.0 million in a license fee and substantive milestone payments including up to $67.0 million for the achievement of development milestones, up to $170.0 million for the achievement of regulatory milestones and up to $80.0 million for the achievement of commercialization milestones. In addition, we are eligible to receive up to $136.5 million in milestone payments for each additional drug successfully developed as well as up to $50.0 million in commercial milestones if a drug using Roche's proprietary brain shuttle technology is successfully commercialized. We are also eligible to receive tiered royalties on any product sales of drugs resulting from this alliance. We will earn the next milestone payment of $22.0 million if we initiate a Phase 1 trial for a drug targeting HTT protein.

During the three and nine months ended September 30, 2013, we earned revenue of $1.9 million and $3.1 million, respectively, from our relationship with Roche. Our balance sheet at September 30, 2013 included deferred revenue of $26.9 million related to the upfront payment.

Table of Contents

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 anemia of chronic disorders, or ACD. 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. Because repayment of the promissory note was uncertain, we did not record any revenue from the upfront payment when we entered into the agreement. In May 2012, Xenon selected XEN701, a drug designed to inhibit the production of hepcidin, as a development candidate. In June 2013, we earned a $2 million license fee when Xenon exercised its option to an exclusive worldwide license to XEN701. In addition, in June 2013 Xenon repaid the $1.5 million convertible promissory note. We recognized the $2 million license fee and the $1.5 million upfront payment as revenue in the second quarter of 2013. Under our collaboration agreement with Xenon, we may receive up to $296 million in substantive milestone payments for the achievement of pre-specified milestone events that are met by two independent products, 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. In addition, we are eligible to receive royalties on future product sales of XEN701 and a portion of sublicense revenue. We will earn the next milestone payment of $3 million if Xenon initiates a Phase 2 clinical trial for XEN701.

During the nine months ended September 30, 2013, we earned revenue of $3.5 million from our relationship with Xenon.

External Project Funding

CHDI Foundation, Inc.

Starting in November 2007, CHDI provided financial and scientific support to our HD drug discovery program through our development collaboration. In April 2013, we formed an alliance with Roche to develop treatments for HD. Under the terms of our agreement with CHDI, we will

reimburse CHDI for a portion of its support of our HD program out of the payments we receive from Roche. In April 2013, we paid CHDI $1.5 million associated with the signing of the Roche agreement which we recorded as research and development expense. In October 2013, we paid CHDI an additional $1.5 million, which we recorded as research and development expense in the third quarter of 2013, because we further progressed our HD program. If we achieve certain milestones under our collaboration with Roche, we will make additional payments to CHDI. During the nine months ended September 30, 2013, we earned revenue of $414,000 from our relationship with CHDI.

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

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

Forward-Looking Statements

In addition to historical information contained in this Report on Form 10-Q, this Report includes forward-looking statements regarding our business, the therapeutic and commercial potential of our technologies and products in development, and the financial position of Isis Pharmaceuticals, Inc. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning our programs are described in additional detail in our Annual Report on Form 10-K for the year ended December 31, 2012, 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 34 of this Report.

Table of Contents

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. Our strategy is to do what we do best—to discover and develop unique antisense drugs. The efficiency and broad applicability of our drug discovery platform allows us to discover and develop antisense drugs to treat a wide range of diseases, including cardiovascular, severe and rare, neurologic and metabolic diseases and cancer.

Our partnering strategy provides us the flexibility to license each of our drugs at the optimal time to maximize the near- and long-term value for each drug. In this way, we can expand our and our partners' pipelines with antisense drugs that we design to address significant medical needs while remaining small and focused. The cash generated from our partnering strategy provides us the financial flexibility to develop our drugs to potentially more valuable stages of clinical development, thereby increasing our share of our drugs' commercial revenues. Our strong financial position is a result of the successful execution of our business strategy as well as our focused research and development capabilities.

Our flagship product, KYNAMRO (mipomersen sodium) injection, is on the market in the United States for patients with homozygous familial hypercholesterolemia, or HoFH. Patients with HoFH are at high cardiovascular risk and cannot reduce their low-density lipoprotein cholesterol, or LDL-C, sufficiently with currently available lipid-lowering therapies. In January 2013, the FDA approved the marketing application for KYNAMRO for patients with HoFH and Genzyme is also pursuing marketing approval in other markets. Genzyme is executing a comprehensive plan to address a global commercial market that consists of patients who are in desperate need of new treatment options. Genzyme has substantial expertise in successfully marketing drugs in the United States and internationally for severe and rare diseases and plans to leverage its infrastructure in these markets. By concentrating marketing and sales efforts on lipid specialists, and physicians who refer patients to these specialists, Genzyme plans to quickly reach patients with HoFH in the United States.

Our pipeline goes well beyond KYNAMRO. We have a pipeline of 30 drugs in development that represents the potential for significant commercial opportunities in many therapeutic areas. We believe that several of the drugs in our pipeline could reach the market by 2017. For instance, we designed our transthyretin, or TTR, amyloidosis and spinal muscular atrophy, or SMA, drugs to treat patients with severe and rare diseases who have very limited therapeutic options. Because of the significant unmet medical need and the severity of these diseases, new therapeutic approaches could warrant an accelerated path to market. In addition, several of the drugs in our pipeline are advancing through Phase 2 clinical programs and could represent significant near and mid-term licensing opportunities. These drugs, including ISIS-CRP_{Rx} and ISIS-FXI_{Rx}, represent substantial commercial opportunities with the potential for Phase 2 data within the next 9 to 15 months. Further, we recently reported encouraging Phase 2 data for ISIS-$APOCIII_{Rx}$ and we plan to advance ISIS-$APOCIII_{Rx}$ into a Phase 3 program early next year. We plan to use the proceeds from our June 2013 public offering of common stock to develop select drugs in our pipeline, such as ISIS-$APOCIII_{Rx}$, to later stages of development prior to partnering.

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 AstraZeneca, Biogen Idec, GlaxoSmithKline, or GSK, and Roche, early in the development of a drug. Typically, the drugs we partner early in development are in therapeutic areas of high risk, like severe neurological diseases, or in areas where Phase 2 results would likely not provide a significant increase in value, like cancer. These preferred partner transactions allow us to develop select drugs that could have significant commercial potential with a knowledgeable and committed partner with the financial resources to fund later-stage clinical studies and expertise to complement our own development efforts. As in our other partnerships, we benefit financially from upfront payments, milestone payments, licensing fees and royalties. This allows us to expand and broaden our drug discovery efforts to new disease targets in therapeutic areas that are outside of our expertise or in areas where our partners will provide tools and resources that will complement our drug discovery efforts. For example, through our oncology partnership with AstraZeneca, we are capitalizing on AstraZeneca's development experience and research in oncology.

The broad applicability of our drug discovery technology and the clinical successes of the drugs in our pipeline continue to create new partnering opportunities. Since January 2012, we have initiated six new partnerships that involve neurological diseases or cancer, including a strategic alliance with Roche to discover and develop antisense drugs to treat Huntington's disease, four strategic alliances with Biogen Idec to discover and develop antisense drugs

for the treatment of neurologic diseases, and a strategic alliance with AstraZeneca to discover and develop antisense drugs to treat cancer. We have received more than $230 million in upfront payments and have the potential to earn nearly $6 billion in future milestone payments and licensing fees from these partnerships. Since 2007, our partnerships have generated an aggregate of more than $1 billion in payments from upfront and licensing fees, equity purchase payments, milestone payments and research and development funding. In addition, for our current partnered programs we have the potential to earn nearly $9 billion in future milestone payments and licensing fees. We also have the potential to share in the future commercial success of our inventions and drugs resulting from these partnerships through earn out, profit sharing, or royalty arrangements.

Table of Contents

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 co-founded with Alnylam focused on microRNA therapeutics. In October 2012, Regulus completed an initial public offering. As of September 30, 2013, the carrying value of our investment in Regulus was $65 million, demonstrating the value of our satellite company strategy. All of these different types of relationships are part of our unique business model and create near and long-term shareholder value.

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. Our 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 Highlights

- We reported encouraging Phase 1 and Phase 2 data on a number of antisense drugs, demonstrating good safety and tolerability profiles with encouraging results in measures of efficacy in multiple disease settings.
    - We reported multiple Phase 2 data sets on ISIS-APOCIII$_{Rx}$ demonstrating that ISIS-APOCIII$_{Rx}$ works in patients with high to severely high triglycerides, including patients with FCS. Treatment with ISIS-APOCIII$_{Rx}$ resulted in significant reductions of apoC-III and triglycerides, and significant increases in HDL-C.
    - Dr. Kathy Swoboda presented follow up data from a single-dose open-label Phase 1 study of ISIS-SMN$_{Rx}$ in children with SMA at the International Congress of the World Muscle Society. In this study, data suggest that children from the two highest doses continued to show improvements in muscle function tests up to 14 months after a single injection of ISIS-SMN$_{Rx}$.
    - We reported Phase 2 data on ISIS-CRP$_{Rx}$ in patients with rheumatoid arthritis, or RA.
- We continued to mature our pipeline by advancing drugs in development and initiating new clinical studies.
    - We advanced the Phase 2/3 study of ISIS-TTR$_{Rx}$, a drug to treat patients with familial amyloid polyneuropathy. As a result, we earned $2 million from GlaxoSmithKline.
    - We advanced the Phase 2 study of ISIS-SMN$_{Rx}$ in infants with SMA. As a result, we earned a $2 million milestone payment from Biogen Idec.
    - We initiated Phase 2 studies on ISIS-GCGR$_{Rx}$ and ISIS-PTP1B$_{Rx}$, all antisense drugs designed to control glucose in patients with type 2 diabetes.
- We and our partners continued to add new drugs to the development pipeline.
    - We and Biogen Idec selected a development candidate, ISIS-DMPK$_{Rx}$, for the treatment of patients with myotonic dystrophy type I. Upon initiation of IND-enabling studies, we earned a $10 million milestone payment from Biogen Idec.
    - GlaxoSmithKline added a development candidate, ISIS-GSK3$_{Rx}$, to its collaboration with us. We earned $7 million in milestone payments from GlaxoSmithKline as a result.
    - Regulus nominated a development candidate, RG-101, to move forward in development for the treatment of patients with hepatitis C virus. This is the first drug targeting a microRNA that Regulus has moved into development.

Corporate Highlights

- We formed a broad strategic alliance with Biogen Idec to discover and develop antisense drugs to treat neurological disorders.
    - We received a $100 million upfront payment from Biogen Idec as part of the collaboration that combines Biogen Idec's expertise in neurology with our leadership in antisense technology to develop novel therapies to treat neurological diseases. We are eligible to receive substantial milestone payments, license fees and royalty payments for all treatments developed through this collaboration.

Table of Contents

Critical Accounting Policies

We prepare our condensed consolidated financial statements in conformity with accounting principles generally accepted in the United States of America. As such, we make certain estimates, judgments and assumptions that we believe are reasonable, based upon the information available to us. These judgments involve making estimates about the effect of matters that are inherently uncertain and may significantly impact our quarterly or annual results of operations and financial condition. Each quarter, our senior management discusses the development, selection and disclosure of such estimates with our audit

committee of our board of directors. There are specific risks associated with these critical accounting policies and we caution that future events rarely develop exactly as one may expect, and that best estimates may require adjustment. A discussion of these specific risks can be found 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, 2012. There have been no material changes to our critical accounting policies and estimates from the information provided in that discussion.

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 the fair value of convertible debt without the conversion feature;
- Determining when we are the primary beneficiary for entities that we identify as variable interest entities; 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.

Results of Operations

Revenue

Revenue for the three and nine months ended September 30, 2013 was $23.6 million and $105.0 million, respectively, compared to $11.6 million and $82.2 million for the same periods in 2012. 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, we earned more than $60 million in revenue from milestone and licensing payments in the first nine months of 2013 including:

- $25 million from Genzyme when the FDA approved the KYNAMRO NDA;
- $10 million when AstraZeneca added a second development candidate, ISIS-AR$_{Rx}$, to its collaboration with us;
- $16.5 million from GlaxoSmithKline because we initiated the Phase 2/3 study of ISIS-TTR$_{Rx}$ and advanced ISIS-GSK3$_{Rx}$ in development;
- $5.5 million from Biogen Idec because we advanced the Phase 2 study of ISIS-SMN$_{Rx}$ in infants; and
- $3.5 million when Xenon licensed XEN701 from us.

Our revenue in the first nine months of 2013 also included more than $33 million in revenue we earned from our alliances with AstraZeneca, Biogen Idec, GlaxoSmithKline and Roche.

Table of Contents

In September 2013, we and Biogen Idec entered into a new strategic neurology collaboration. As part of this collaboration, we received a $100 million upfront payment, which we will begin amortizing into revenue over six years starting in October 2013. In addition in the fourth quarter of 2013, we have already earned $10 million in a milestone payment for advancing ISIS-DMPK$_{Rx}$ in development.

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for the three and nine months ended September 30, 2013 was $23.4 million and $102.9 million, respectively, compared to $11.1 million and $80.1 million for the same periods in 2012. The increase in the first nine months of 2013 was primarily due to an increase in milestone payments compared to the same period in 2012 and more than $33 million in revenue we earned from our alliances with AstraZeneca, Biogen Idec, GlaxoSmithKline and Roche.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties for the three and nine months ended September 30, 2013 was $202,000 and $2.1 million, respectively, and was essentially flat when compared to $474,000 and $2.1 million for the same periods in 2012.

Operating Expenses

As projected, operating expenses of $49.1 million and $136.8 million, respectively, for the three and nine months ended September 30, 2013 were moderately higher compared to $39.6 million and $125.0 million for the same periods in 2012. Expenses in the first nine months of 2013 were higher primarily due to higher development costs associated with the progression of several of the drugs in our pipeline into later stage clinical trials.

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, Development and Patent Expenses

Our research, development and patent 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, development and patent expenses (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2013	2012	2013	2012
Research, development and patent expenses	$ 43,287	$ 34,831	$ 119,432	$ 109,972
Non-cash compensation expense related to equity awards	2,373	1,720	7,171	5,728
Total research, development and patent expenses	$ 45,660	$ 36,551	$ 126,603	$ 115,700

As projected, research, development and patent expenses of $43.3 million and $119.4 million for the three and nine months ended September 30, 2013, respectively, were moderately higher compared to $34.8 million and $110.0 million for the same periods in 2012. Research, development and patent expenses in the first nine months of 2013 were higher primarily due to higher development costs associated with the progression of several of the drugs in our pipeline into later stage clinical trials. All amounts exclude non-cash compensation expense related to equity awards.

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

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2013	2012	2013	2012
Antisense drug discovery expenses	$ 9,503	$ 8,250	$ 29,754	$ 25,044
Non-cash compensation expense related to equity awards	667	499	2,118	1,663
Total antisense drug discovery	$ 10,170	$ 8,749	$ 31,872	$ 26,707

Antisense drug discovery costs for the three and nine months ended September 30, 2013 were $9.5 million and $29.8 million, respectively, compared to $8.3 million and $25.0 million for the same periods in 2012. Expenses increased in 2013 compared to 2012 primarily due to a $1.5 million payment we made to CHDI in the second quarter of 2013 and due to additional supplies used in our research activities. Under the terms of our agreement with CHDI, we reimbursed CHDI for a portion of its support of our HD program out of the $30 million upfront payment we received from our alliance with Roche to develop treatments for HD. 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 September 30,		Nine Months Ended September 30,	
	2013	2012	2013	2012
KYNAMRO	$ 2,913	$ 2,593	$ 6,504	$ 8,060
ISIS-TTR$_{Rx}$	1,534	788	3,519	3,332
Other antisense development products	15,453	10,188	39,041	34,337
Development overhead costs	1,982	1,555	5,542	5,005
Non-cash compensation expense related to equity awards	741	589	2,317	1,970
Total antisense drug development	$ 22,623	$ 15,713	$ 56,923	$ 52,704

Antisense drug development expenses were $21.9 million and $54.6 million for the three and nine months ended September 30, 2013, respectively, compared to $15.1 million and $50.7 million for the same periods in 2012. Expenses increased in 2013 compared to 2012 primarily due to costs associated with the progression of several of the drugs in our pipeline into later stage clinical trials. These increases were offset, in part, by a decrease in expenses related to KYNAMRO. 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 in which we continually adjust the development strategy for each product. Although we may characterize a product as "in Phase 1" or "in Phase 2," it does not mean that we are conducting a single, well-defined study with

dedicated resources. Instead, we allocate our internal resources on a shared basis across numerous products based on each product's particular needs at that time. This means we are constantly shifting resources among products. Therefore, what we spend on each product during a particular period is usually a function of what is required to keep the products progressing in clinical development, not what products we think are most important. For example, the number of people required to start a new study is large, the number of people required to keep a study going is modest and the number of people required to finish a study is large. However, such fluctuations are not indicative of a shift in our emphasis from one product to another and cannot be used to accurately predict future costs for each product. And, because we always have numerous products in preclinical and early stage clinical research, the fluctuations in expenses from product to product, in large part, offset one another. If we partner a drug, it may affect the size of a trial, its timing, its total cost and the timing of the related costs. As part of our collaboration with Genzyme, we have transitioned development responsibility for KYNAMRO to Genzyme. We and Genzyme share development costs equally until KYNAMRO is profitable.

Table of Contents

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 September 30,		Nine Months Ended September 30,	
	2013	2012	2013	2012
Manufacturing and operations	$ 5,454	$ 4,624	$ 14,029	$ 14,309
Non-cash compensation expense related to equity awards	306	232	965	797
Total manufacturing and operations	$ 5,760	$ 4,856	$ 14,994	$ 15,106

Manufacturing and operations expenses of $5.5 million and $14.0 million for the three and nine months ended September 30, 2013, respectively, decreased slightly compared to $4.6 million and $14.3 million for the same periods in 2012. All amounts exclude non-cash compensation expense related to equity awards.

R&D Support

In our research, development and patent 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 expenses (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2013	2012	2013	2012
Personnel costs	$ 2,291	$ 2,252	$ 6,946	6,792
Occupancy	1,787	1,767	5,121	5,170
Patent expenses	695	988	3,769	2,334
Depreciation and amortization	589	773	1,886	2,371
Insurance	273	286	840	866
Other	813	767	2,481	2,352
Non-cash compensation expense related to equity awards	659	400	1,771	1,298
Total R&D support	$ 7,107	$ 7,233	$ 22,814	$ 21,183

R&D support costs for the three and nine months ended September 30, 2013 were $6.4 million and $21.0 million, respectively, compared to $6.8 million and $19.9 million for the same periods in 2012. Expenses increased in the first half of 2013 compared to the same period in 2012 primarily due to litigation costs for our patent infringement lawsuit against Santaris Pharma A/S. All amounts exclude non-cash compensation expense related to equity awards.

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.

Table of Contents

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2013	2012	2013	2012

General and administrative expenses	$ 2,991	$ 2,782	$ 9,094	$ 8,248
Non-cash compensation expense related to equity awards	439	314	1,147	1,033
Total general and administrative	$ 3,430	$ 3,096	$ 10,241	$ 9,281

General and administrative expenses of $3.0 million and $9.1 million for the three and nine months ended September 30, 2013, respectively, were slightly higher compared to $2.8 million and $8.2 million for the same periods in 2012 primarily due to higher personnel expenses. All amounts exclude non-cash compensation expense related to equity awards.

Equity in Net Loss of Regulus Therapeutics Inc.

We did not recognize any equity in net loss of Regulus for the three and nine months ended September 30, 2013, compared to equity in net loss of Regulus of $1.1 million for the nine months ended September 30, 2012. We used the equity method of accounting to account for our investment in Regulus until Regulus' IPO in October 2012. In the fourth quarter of 2012, we began accounting for our investment at fair value because we now own less than 20 percent of Regulus' common stock and we no longer have significant influence over the operating and financial policies of Regulus.

Investment Income

Investment income for the three and nine months ended September 30, 2013 was $434,000 and $1.4 million, respectively, compared to $408,000 and $1.5 million for the same periods in 2012.

Interest Expense

Interest expense includes non-cash amortization of the debt discount and debt issuance costs on our convertible notes, non-cash interest expense related to the long-term financing liability for our primary facility, and interest expense payable in cash for our convertible notes and other miscellaneous debt related items.

The following table sets forth information on interest expense (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2013	2012	2013	2012
Convertible Notes:				
Non-cash amortization of debt discount and debt issuance costs	$ 1,711	$ 3,355	$ 5,022	$ 8,192
Interest expense payable in cash	1,383	789	4,151	2,922
Non-cash interest expense for long-term financing liability	1,644	1,627	4,919	4,871
Other	129	166	378	350
Total interest expense	$ 4,867	$ 5,937	$ 14,470	$ 16,335

Interest expense for the three and nine months ended September 30, 2013 was $4.9 million and $14.5 million, respectively, compared to $5.9 million and $16.3 million for the same periods in 2012. The decrease in interest expense was primarily due to a decrease in amortization of debt discount related to our convertible notes. We record non-cash amortization of debt discount on our convertible notes because we account for our convertible notes by separating the liability and equity components of the instrument in a manner that reflects our nonconvertible debt borrowing rate. As a result, we assign a value to the debt component of our convertible notes equal to the estimated fair value of similar debt instruments without the conversion feature, which means we record the debt instruments at a discount that we amortize over the life of the notes as non-cash interest expense. We are using an eight percent borrowing rate for the $2^{3}/_{4}$ percent convertible senior notes compared to a 9.3 percent borrowing rate for the $2^{5}/_{8}$ percent convertible subordinated notes that we redeemed in September 2012. The borrowing rate for our $2^{3}/_{4}$ percent notes is less than the rate for our $2^{5}/_{8}$ percent notes because of an improvement in our financial strength and market conditions at the time of each issuance. As a result, we are amortizing less debt discount for the $2^{3}/_{4}$ percent notes compared to the $2^{5}/_{8}$ percent notes. This decrease is partially offset by an increase in interest expense payable in cash because the interest rate is higher on our $2^{3}/_{4}$ percent notes compared to our $2^{5}/_{8}$ percent notes.

Table of Contents

Gain on Investments, net

Gain on investments for the three and nine months ended September 30, 2013 was $175,000 and $2.1 million, respectively, compared to a net gain of $19,000 for the nine months ended September 30, 2012. The gain on investments in the first nine months of 2013 was primarily due to $1.1 million we received in the first quarter of 2013 when we sold the stock we held in Sarepta Therapeutics, Inc. and the $844,000 payment we received from Pfizer, Inc. in the second quarter of 2013 related to its acquisition of Excaliard Pharmaceuticals, Inc. These gains demonstrate the value that we are realizing from our satellite company strategy.

Income Tax Benefit

We recognized a tax benefit of $5.2 million and $6.4 million for the three and nine months ended September 30, 2013, respectively, compared to a tax benefit of $706,000 and $704,000 for the same periods in 2012. The tax benefit we recorded in 2013 is primarily related to the unrealized gain on our investment in Regulus, which reflects the increase in Regulus' stock price this year.

Net Loss and Net Loss per Share

Net loss for the three and nine months ended September 30, 2013 was $24.6 million and $36.4 million, respectively, compared to $37.6 million and $62.8 million for the same periods in 2012. Basic and diluted net loss per share for the three and nine months ended September 30, 2013 were $0.21 per share and $0.33 per share, respectively, compared to $0.37 per share and $0.63 per share for the same periods in 2012. Our net loss for the nine months ended September 30, 2013 decreased compared to 2012 primarily due to the increase in the amount of revenue we earned from our partners in the first nine months

of 2013, offset in part, by a moderate increase in operating expenses. In addition, our income tax benefit in 2013 increased by $5.7 million compared to 2012. Also contributing to the decrease in our net loss was a $4.8 million loss on the early retirement of our 2 5/8% convertible subordinated notes that we recorded in 2012 when we successfully refinanced our convertible debt.

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 September 30, 2013 we have earned approximately $1.2 billion in revenue from contract research and development and the sale and licensing of our intellectual property. From the time we were founded through September 30, 2013, we have raised net proceeds of approximately $1.1 billion from the sale of our equity securities and we have borrowed approximately $786.9 million under long-term debt arrangements to finance a portion of our operations.

As of September 30, 2013, we had cash, cash equivalents and short-term investments of $670.9 million and stockholders' equity of $401.4 million. In comparison, we had cash, cash equivalents and short-term investments of $374.4 million and stockholders' equity of $182.8 million at December 31, 2012. We received a substantial amount of cash in the first nine months of 2013, including:

- $197.4 million in payments from our partners, including the $100 million upfront payment we received from our recently announced strategic collaboration with Biogen Idec;
- $173.2 million in net proceeds from a public offering of our common stock; and
- $56.9 million in proceeds from stock option exercises.

At September 30, 2013, we had consolidated working capital of $660.0 million, compared to $349.1 million at December 31, 2012. Our working capital increased in 2013 primarily due to the increase in cash and the increase in the value of our ownership in Regulus. At September 30, 2013, the carrying value of our investment in Regulus increased to $65.0 million compared to $33.6 million at December 31, 2012.

In June 2013, we completed the sale of 9,617,869 shares of our common stock through a public offering at a price of $19.00 per share, which included 617,869 additional shares sold pursuant to an option we granted to the underwriters. We received net proceeds of approximately $173.2 million from the sale of these shares net of underwriting discounts and commissions and other estimated offering expenses of $9.5 million. We plan to use the proceeds from this offering to increase our drug development activities, including advancing ISIS-APOCIII$_{Rx}$ into a Phase 3 program early next year.

Table of Contents

As of September 30, 2013, our debt and other obligations totaled $283.4 million, and were essentially flat, compared to $284.1 million at December 31, 2012. In June 2013, we drew down $2.5 million on our equipment financing arrangement and this increase was partially offset by rent and principal payments we made in the first nine months of 2013 on our lease obligations and notes payable.

The following table summarizes our contractual obligations as of September 30, 2013. The table provides a breakdown of when obligations become due. We provide a more detailed description of the major components of our debt in the paragraphs following the table:

	Payments Due by Period (in millions)				
Contractual Obligations (selected balances described below)	**Total**	**Less than 1 year**	**1-3 years**	**3-5 years**	**After 5 years**
2 3/4 percent Convertible Senior Notes (principal and interest payable)	$ 237.2	$ 5.4	$ 11.1	$ 11.1	$ 209.6
Facility Rent Payments	$ 139.4	$ 6.1	$ 12.7	$ 13.4	$ 107.2
Equipment Financing Arrangements (principal and interest payable)	$ 9.1	$ 4.8	$ 4.3	$ —	$ —
Other Obligations (principal and interest payable)	$ 1.4	$ 0.1	$ 0.1	$ 0.1	$ 1.1
Capital Lease	$ 0.4	$ 0.2	$ 0.2	$ —	$ —
Operating Leases	$ 26.9	$ 1.5	$ 3.0	$ 2.9	$ 19.5
Total	$ 414.4	$ 18.1	$ 31.4	$ 27.5	$ 337.4

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 August 2012, we completed a $201.3 million convertible debt offering, which raised proceeds of approximately $194.7 million, net of $6.6 million in issuance costs. The $201.3 million of convertible senior notes mature in 2019 and bear interest at 2¾ percent, which is payable semi-annually. We used a substantial portion of the net proceeds from the issuance of these notes to redeem the entire $162.5 million in principal of our 2⅝ percent convertible subordinated notes. The 2¾ percent notes are convertible under certain conditions, at the option of the note holders, into approximately 12.1 million shares of our common stock at a conversion price of $16.63 per share. We will settle conversions of the notes, at our election, in cash, shares of our common stock or a combination of both. We can redeem the 2¾ percent notes at our option, in whole or in part, on or after October 5, 2016 if the last reported sale price of our common stock for at least 20 trading days (whether or not consecutive) during the period of 30 consecutive trading days ending on the trading day immediately preceding the date we provide the redemption notice exceeds 130 percent of the applicable conversion price for the 2¾ percent notes on each such day. The redemption price for the 2¾ percent notes will equal 100 percent of the principal amount being redeemed, plus accrued and unpaid interest, plus $90 per each $1,000 principal amount being redeemed. Holders of the 2¾ percent notes may require us to purchase some or all of their notes upon the occurrence of certain fundamental changes, as set forth in the indenture governing the 2¾ percent notes, at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus accrued and unpaid interest.

In October 2008, we entered into an equipment financing loan agreement 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 and in June 2013 we drew down $2.5 million in principal at an interest rate of 4.38 percent. As of September 30, 2013, our outstanding borrowings under this loan agreement were at a weighted average interest rate of 4.34 percent and we can borrow up to an additional $3.4 million in principal to finance the purchase of equipment until April 2014. The carrying balance under this loan agreement at September 30, 2013 and December 31, 2012 was $8.7 million and $10.0 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 this lease is based on a percentage of the total construction costs spent by BioMed to acquire the land and build the new facility. To gain early access to the facility, 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. We are depreciating the building over its economic life and we will apply our rent payments, which began on January 1, 2012, against the liability over the term of the lease.

Table of Contents

In addition to contractual obligations, we had outstanding purchase orders as of September 30, 2013 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, 2012.

Risks Associated with our Drug Discovery and Development Business

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

Even though KYNAMRO is approved for HoFH in the United States, and if any of our other drugs is approved for marketing, our success will depend upon the medical community, patients and third party payors accepting our drugs as medically useful, cost-effective and safe. Even when the FDA or foreign regulatory authorities approve our or our partners' drugs for commercialization, doctors may not use our drugs to treat patients. We and our partners may not successfully commercialize additional drugs.

In particular, even though KYNAMRO is approved for HoFH in the United States it may not be commercially successful.

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 received for KYNAMRO or our other drugs or increase patient coinsurance to a level that makes KYNAMRO or our other drugs unaffordable.

Table of Contents

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 or commercialization strategy that competes with our strategy for KYNAMRO. Other companies are currently developing products that could compete with KYNAMRO. Products such as microsomal triglyceride transfer protein inhibitors, or MTP inhibitors, and other lipid lowering drugs other companies are developing or commercializing could potentially compete with KYNAMRO. For example, Aegerion Pharmaceuticals, Inc. received approval from the FDA and the European Medicines Agency to market its MTP inhibitor, lomitapide, as an adjunct to a low-fat diet and other lipid-lowering treatments in patients with HoFH. Our revenues and financial position will suffer if KYNAMRO cannot compete effectively in the marketplace.

Following approval, KYNAMRO is, and any of our other drugs could be subject to regulatory limitations.

Following approval of a drug, we and our partners must comply with comprehensive government regulations regarding the manufacture, marketing and distribution of drug products. Even if approved, we or our partners 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. For example:

- KYNAMRO is approved in the United States as an adjunct to lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol, apolipoprotein B, total cholesterol, and non-high density lipoprotein-cholesterol in patients with HoFH;
- the KYNAMRO label contains a Boxed Warning citing a risk of hepatic toxicity; and
- KYNAMRO is available only through a Risk Evaluation and Mitigation Strategy called the KYNAMRO REMS.

In addition, when 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.

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 or our partners may lose regulatory approval, or we or our partners may need to conduct additional clinical studies and/or change the labeling of our drug products including KYNAMRO.

Table of Contents

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 additional 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 rely on Genzyme to manufacture the finished drug product for KYNAMRO, including the initial commercial launch supply. In addition, Genzyme is 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.

If we or our partners fail to obtain regulatory approval for our drugs, including additional approvals for KYNAMRO, we or our partners cannot sell them in the applicable markets.*

We cannot guarantee that any of our drugs will be safe and effective, or will be approved for commercialization. In addition, we cannot guarantee that KYNAMRO will be approved outside the United States or for additional indications. 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 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. It is possible that other 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 or harm commercialization of the drug. For example, in March 2013 the CHMP of the European Medicines Agency maintained a negative opinion for Genzyme's marketing authorization application for KYNAMRO as a treatment for patients with HoFH.

Failure to receive marketing approval for our drugs, including KYNAMRO outside the United States, 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.

Table of Contents

If the results of clinical testing indicate that any of our drugs 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 are safe and effective for human use, we may need to abandon one or more of our drug development programs. There are ongoing clinical studies for KYNAMRO and sales to patients, adverse events from which could negatively impact our pending or planned marketing approval applications and commercialization of KYNAMRO.

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

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 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.

Table of Contents

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 the ongoing 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 any expanded product label for 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 September 30, 2013, we had an accumulated deficit of approximately $943.3 million and stockholders' equity of approximately $401.4 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from research grants and the sale or licensing of our patents, as well as interest income. We 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 AstraZeneca, ATL, Atlantic Pharmaceuticals, Biogen Idec, iCo, Genzyme, GSK, OncoGenex, Pfizer, Teva Pharmaceutical Industries Ltd., and Xenon. If any of these pharmaceutical companies stops developing and/or funding these drugs, our business could suffer and we may not have, or be willing to dedicate, the resources available to develop these drugs on our own.

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

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

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

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

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

Table of Contents

For example, a collaborator such as AstraZeneca, Biogen Idec, Genzyme, or GSK, 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 additional approvals or sales expectations of KYNAMRO, the price of our securities would likely decrease.

For example, in March 2013 the CHMP of the European Medicines Agency maintained a negative opinion for Genzyme's marketing authorization application for KYNAM RO as a treatment for patients with HoFH.

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 successful commercialization. As of September 30, 2013, we had cash, cash equivalents and short-term investments equal to $670.9 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:

Table of Contents

- additional marketing approvals 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 September 30, 2013, the market price of our common stock ranged from $7.56 to $39.83 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, including potential product liability claims related to KYNAMRO. 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.

Table of Contents

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 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 and 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 or otherwise affects our business, 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. In addition, our development and commercialization activities could be harmed or delayed by a shut down of the U.S. government including the FDA.

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.

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.

Table of Contents

The provisions of our convertible senior 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 may issue approximately 12.1 million shares of our common stock upon conversion of our convertible senior 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.

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.

Table of Contents

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. We conducted our evaluation following the 1992 Internal Control—Integrated Framework set forth by the Committee of Sponsoring Organizations of the Treadway Commission. Based on this evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of September 30, 2013. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to September 30, 2013.

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 we are required to disclose 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. We designed and evaluate our disclosure controls and procedures recognizing that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance 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 September 2012, the court denied Santaris' motion for summary judgment and opened limited discovery related to whether Santaris' alleged infringing activities are permitted by the safe harbor under 35 U.S.C. Section 271(e)(1). In April 2013, we amended our complaint related to the lawsuit to include additional claims alleging that Santaris' activities providing antisense drugs and antisense drug discovery services to a pharmaceutical company infringes U.S. Patent No. 6,440,739 entitled "Antisense Modulation of Glioma-Associated Oncogene-2 Expression"; and that Santaris induced its actual and prospective pharmaceutical partners to infringe U.S. Patent No. 6,326,199.

In August 2013, Gilead Sciences Inc. filed a suit in the United States District Court of the Northern District of California related to United States Patent Nos. 7,105,499 and 8,481,712 that are jointly owned by Merck Sharp & Dohme Corp. and Isis Pharmaceuticals, Inc. In the suit Gilead is asking the court to determine that Gilead's activities do not infringe the named patents or that the patents are not valid. Isis' answer is due in November 2013. Merck is responsible for the costs associated with this suit.

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

Not applicable

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable

Table of Contents

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable

ITEM 5. OTHER INFORMATION

Not applicable

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.1	Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement between the Registrant and Biogen Idec MA Inc. dated September 5, 2013. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.2	Amendment #1 to Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated August 13, 2013. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.3	Amendment Number Three to the Amended and Restated License and Collaboration Agreement among the Registrant, Alnylam Pharmaceuticals, Inc. and Regulus Therapeutics Inc. dated August 2, 2013. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.4	Registrant's Amended and Restated Isis Pharmaceuticals, Inc. 10b5-1 Trading Plan dated September 12 2013.
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 September 30, 2013, formatted in Extensive Business Reporting Language (XBRL): (i) condensed consolidated balance sheets, (ii) condensed consolidated statements of operations, (iii) condensed consolidated statements of comprehensive income (loss), (iv) condensed consolidated statements of cash flows and (v) notes to condensed consolidated financial statements (detail tagged).

Isis Pharmaceuticals, Inc.

(Registrant)

Table of Contents

SIGNATURES

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

Signatures	Title	Date
/s/ Stanley T. Crooke Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	November 5, 2013
/s/ Elizabeth L. Hougen Elizabeth L. Hougen	Senior Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	November 5, 2013

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

STRATEGIC NEUROLOGY DRUG DISCOVERY AND DEVELOPMENT COLLABORATION, OPTION AND LICENSE AGREEMENT

BETWEEN

ISIS PHARMACEUTICALS, INC.,

AND

BIOGEN IDEC MA INC.

STRATEGIC NEUROLOGY DRUG DISCOVERY AND DEVELOPMENT COLLABORATION, OPTION AND LICENSE AGREEMENT

This STRATEGIC NEUROLOGY DRUG DISCOVERY AND DEVELOPMENT COLLABORATION, OPTION AND LICENSE AGREEMENT (the "***Agreement***") is entered into as of the 5th day of September, 2013 (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 possesses certain Patent Rights, Know-How, technology and expertise with respect to antisense therapeutics, and has novel and valuable capabilities for the research, discovery, identification, synthesis and development of antisense therapeutics;

WHEREAS, Biogen Idec has expertise in developing and commercializing human therapeutics, and is interested in entering into a strategic relationship with Isis to explore potential targets for the treatment of neurological and neuromuscular diseases and to create antisense and other drugs to such targets;

WHEREAS, Biogen Idec and Isis now desire to enter into a new strategic collaboration in neurological and neuromuscular diseases to include (i) a neurological disease research program focused on the identification, validation, and applications of novel targets, (ii) a broad core technology research program focused on enhancing the Parties' knowledge of antisense oligonucleotide pharmacokinetics and pharmacodynamics in the central and peripheral nervous systems, (iii) a targeted drug discovery and development effort, and (iv) the exclusive opportunity for Biogen Idec to select collaboration targets from among all available targets reaching target sanction status in Isis' neurology program;

WHEREAS, with regard to certain neurology targets Biogen Idec selects as collaboration targets for development using an antisense molecule, Biogen Idec desires Isis to (i) identify a development candidate for each of the collaboration targets, (ii) develop the development candidate through completion of the first clinical trial designed to demonstrate proof of mechanism or proof of therapeutic benefit, and (iii) provide Biogen Idec an option to obtain an exclusive license under this Agreement to develop, manufacture and commercialize collaboration products in the field; and

WHEREAS, for certain neurology targets relating to ALS, the Parties will collaborate to develop and identify antisense and other drugs to such targets as provided herein;

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. **Collaboration Overview**.

1.1.1. The intent of the Collaboration is for the Parties to conduct (i) a neurological disease research program focused on the identification, validation, and applications of novel Neurology Targets, (ii) a broad core technology research program focused on enhancing the Parties' knowledge of ASO pharmacokinetics and pharmacodynamics in the central and peripheral nervous systems, and (iii) an expanded drug discovery and development effort in Neurological Disease, including a program specifically focused on certain ALS Targets. This Agreement also provides Biogen Idec the exclusive opportunity to select Collaboration Targets and Biogen Idec Alternate Modality Targets from among all available Neurology Targets Isis is independently researching up through Target Sanction.

1.1.2. Once a Neurology Target reaches Target Sanction, the Neurology Target may be selected as a Collaboration Target, a Biogen Idec Alternate Modality Target or both under this Agreement. Isis will generate at least one Development Candidate, if feasible for each Collaboration Program that is not focused on an ALS Target; and advance each such Development Candidate through the completion of the first PoC Trial under the applicable Collaboration Program.

1.1.3. When an ALS Target is selected as a Collaboration Target, Isis will generate at least one Development Candidate, if feasible, for each ALS Collaboration Program; and Biogen Idec will use Commercially Reasonable Efforts to advance each such Development Candidate through at least the completion of the first PoC Trial under the applicable Collaboration Program.

1.1.4. Isis will provide Biogen Idec an option to further Develop and ultimately Commercialize (I) Compounds and Collaboration Products under such Collaboration Programs, (II) Biogen Idec Alternate Modality Products or (III) both Collaboration Products and Biogen Idec Alternate Modality Products, in each case, under an exclusive license from Isis.

1.1.5. The Parties have agreed to form a collaboration steering committee to oversee the Collaboration under this Agreement, a joint research committee reporting to the CSC to oversee the Core Research Program, the Neurological Disease Research Program, and each ASO Development Candidate Identification Plan, and one or more joint development committees reporting to the CSC to oversee the development activities for Development Candidates.

1.1.6. The purpose of this Section 1.1 is to provide a high-level overview of the roles, responsibilities, rights and obligations of each Party under this Agreement, and therefore this Section 1.1 is qualified in its entirety by the more detailed provisions of this Agreement set forth below.

1.2. **Research Programs**. Subject to and in accordance with the terms of this Agreement, during the Research Term, Isis and Biogen Idec will conduct two research programs, each under a separate mutually agreed plan. The first research program will cover research focused on enhancing the Parties' knowledge of ASO pharmacokinetics and pharmacodynamics in the central and peripheral nervous systems (such program, the "***Core Research Program***" and the plan for such program, the "***Core Research Plan***"). The second research program will focus on the identification and validation of High Interest Targets, and the identification of ALS Targets, that are eligible to become Collaboration Targets (such program, the "***Neurological Disease Research Program***" and the plan for such program, the "***Neurological Disease Research Plan***"). Drafts of the Core Research Plan and the initial Neurological Disease Research Plan have been mutually agreed upon by the Parties in writing on or prior to the Effective Date. The Parties will finalize these initially agreed draft plans within [***] days after the Effective Date. Thereafter, the Parties will update such plans at least once before the beginning of each Calendar Year, and submit them to the Neurology JRC for its review and approval. Each update to the Neurological Disease Research Plan will include, at a minimum (i) the activities to support Target Sanction in the Calendar Year covered by such Neurological Disease Research Plan, (ii) any Neurological Disease research to support Collaboration Programs, and (iii) any ongoing work on High Interest Targets from prior Calendar Years. *Notwithstanding the foregoing*, neither Party will be required to complete any activities under the Core Research Plan or Neurological Disease Research Plan if such Party in good faith believes that such activities are not technically feasible given the then-current state of the art.

1.2.1. **Research Term**. The term for the conduct of the Core Research Program and the Neurological Disease Research Program will begin on the Effective Date and will end on the sixth anniversary of the Effective Date (the "***Research Term***"); *provided, however*, that (a) with respect to the Neurological Disease Research Program, (i) Isis will not be required to begin target validation activities under the Neurological Disease Research Program (A) after the [***] anniversary of the Effective Date for any target that is not an ALS Target or (B) after the [***] anniversary of the Effective Date for any ALS Target, in each case, unless otherwise agreed to by the Parties and (ii) if any target validation activities that are Isis Activities are ongoing under the Neurology Disease Research Plan on such sixth anniversary, Isis will complete such activities in accordance with the Neurological Disease Research Plan, and the Research Term will be extended until the completion thereof and (b) with respect to the Core Research Program, Isis will complete all Isis Activities under the Core Research Plan that are ongoing on such sixth anniversary in accordance with such plan, and the Research Term will be extended until the completion thereof.

1.2.2. **Core Research Program**. The Core Research Program activities will focus primarily on investigating and optimizing delivery of ASOs to the CNS. Isis will use Commercially Reasonable Efforts to conduct the Isis Activities under the Core Research Program, and Biogen Idec will use Commercially Reasonable Efforts to conduct the Biogen Idec Activities under the Core Research Program. The Neurology JRC will update the Core Research Plan as needed during the Research Term.

1.2.3. **Neurological Disease Research Program**. The Neurological Disease Research Program activities will focus primarily on identifying and validating novel Neurology Targets and prioritizing a list of High Interest Targets (defined below), including ALS Targets.

(a) ***High Interest Targets***. Under the Neurological Disease Research Plan, Biogen Idec will establish a prioritized list of Neurology Targets, including ALS Targets to designate as high interest targets (each such target, a "***High Interest Target***" and such list the "***High Interest Target List***"). The number of High Interest Targets cannot exceed [***]. The initial High Interest Target List has been mutually agreed upon by the Parties in writing on or prior to the Effective Date. Biogen Idec will present updates, if any, to the High Interest Target List at each meeting of the Neurology JRC. Each Neurology Target added to the High Interest Target List will be a High Interest Target; *provided however*, that if Isis notifies Biogen Idec within [***] days after the date on which Isis receives a High Interest Target List containing a new High Interest Target that (1) [***], (2) such gene target is not eligible to become a High Interest Target hereunder [***], or (3) such gene target is [***], then the applicable gene target will not be a High Interest Target hereunder. When Biogen Idec adds a Neurology Target to the High Interest Target List, Biogen Idec will identify on the High Interest Target List if Biogen Idec intends such target to be an ALS Target. Biogen Idec may convert an ALS Target into a High Interest Target that is not an ALS Target at any meeting of the Neurology JRC. For clarity, Biogen Idec may add any Isis Neurology Target to the High Interest Target List so long as such Isis Neurology Target is more than [***] months away from the date on which Isis in good faith believes [***]. In addition, once target validating activities for a High Interest Target have been initiated under the Neurological Disease Research Plan or by Isis independently (as presented by Isis to the Neurology JRC), Biogen Idec may not remove a High Interest Target from the High Interest Target List until [***].

(b) ***Multi-Indication Targets***. No later than [***] days following the addition of a particular High Interest Target to the High Interest Target List, Isis may notify Biogen Idec in writing that Isis believes, in good faith, based upon published scientific

literature or the results of Isis'

internal research efforts, that such High Interest Target may have therapeutic benefit beyond Neurological Disease (each such High Interest Target, a "***Multi-Indication Target***", and each such notice a "***Multi-Indication Target Notice***"). The Multi-Indication Target Notice will (i) include materials supporting Isis' belief that such High Interest Target may have therapeutic benefit beyond Neurological Disease and (ii) specify whether Isis in good faith believes such Multi-Indication Target is a Primarily Neuro Multi-Indication Target, Equal Multi-Indication Target or Primarily Other Multi-Indication Target. If within [***] days of its receipt of a Multi-Indication Target Notice Biogen Idec notifies Isis in writing that Biogen Idec wishes to remove the applicable Multi-Indication Target from the High Interest Target List, then such Multi-Indication Target will not be a High Interest Target but will continue to be a Neurology Target unless and until its status changes by operation of this Agreement. If Biogen Idec does not so notify Isis that it wishes to remove the applicable Multi-Indication Target from the High Interest Target List within such [***] day period, within [***] days after Biogen Idec's receipt of the applicable Multi-Indication Target Notice, Biogen Idec will notify Isis whether it agrees with Isis' determination as to whether the applicable Multi-Indication Target is a Primarily Neuro Multi-Indication Target, Equal Multi-Indication Target or Primarily Other Multi-Indication Target. If Biogen Idec and Isis agree with respect to such determination, then the agreed upon designation will be binding upon the Parties with respect to such Multi-Indication Target and the provisions of clauses (b)-(e) of APPENDIX 3 will apply with respect to such Multi-Indication Target. If Biogen Idec does not agree with such determination, the Multi-Indication Target will be designated as a Primarily Neuro Multi-Indication Target, Equal Multi-Indication Target or Primarily Other Multi-Indication Target in accordance with Section 1.2.3(d) upon the Neurology JRC agreeing to conduct target validating activities for such Multi-Indication Target under the Neurological Disease Research Plan pursuant to Section 1.2.3(d) and prior to the commencement of such activities. For the avoidance of doubt, if Isis fails to deliver a Multi-Indication Target Notice within [***] days after the addition of a particular High Interest Target to the High Interest Target List, such High Interest Target will not be a Multi-Indication Target hereunder.

(c) ***Target Validation Under the Neurological Disease Research Program***. The Neurology JRC will agree on an update to the Neurological Disease Research Plan annually. The first [***] years of the Research Term are planned to focus on validating the role of novel Neurology Targets that are not ALS Targets in Neurological Disease, with the goal of achieving Target Sanction for High Interest Targets, and providing for all pre-clinical development work under the Neurology Disease Research Plan required to validate such High Interest Targets. Biogen Idec will have

final decision-making authority with respect to [***]. The Neurology JRC will determine the number of High Interest Targets for which activities to support Target Sanction will be conducted during each Calendar Year of the Research Term, which number will, with respect to Collaboration Targets that are not ALS Targets, be no less than [***] and will reflect the number of targets the Neurology JRC determines that Isis can, in the exercise of Commercially Reasonable Efforts, (i) [***], (ii) [***], (iii) [***], and taking into account resources that may be used for ALS Targets, in each case using the number of FTEs provided for under Section 1.11. Prior to the initiation of any activities to support Target Sanction with respect to any High Interest Target, Biogen Idec will notify Isis if such High Interest Target is a Neurology Target with respect to which Biogen Idec has [***] intended for a neurology indication (a ***"Pre-Existing Target"***). Isis will use Commercially Reasonable Efforts to conduct such activities to support Target Sanction on such High Interest Targets each year during the Research Term. The Neurological Disease Research Plan will identify which Party will be responsible for the activities related to validation of such targets. It is anticipated that Biogen Idec will perform the [***] required under the Neurological Disease Research Plan where Biogen Idec, at such time, already has in place at Biogen Idec or through its collaborators the appropriate [***] and the ability to conduct such [***]; and that all other such [***] will be conducted by Isis. Each Party will be responsible for the cost of the work it conducts under the Neurological Disease Research Program as more specifically detailed in Section 1.12 and Section 1.13. Neither Party will be required to conduct work using [***] that are not similar in cost or technical feasibility to the [***] such Party has obtained from Third Parties and uses for its other programs.

(d) ***Target Validation for Multi-Indication Targets*****.** If the Neurology JRC agrees to conduct target validating activities under the Neurological Disease Research Plan with respect to any Multi-Indication Target that the Parties did not agree to designate as a Primarily Neuro Multi-Indication Target, Equal Multi-Indication Target or Primarily Other Multi-Indication Target pursuant to Section 1.2.3(b), within [***] days after such agreement, the CSC will meet to determine whether such target is a Primarily Neuro Multi-Indication Target, Equal Multi-Indication Target or Primarily Other Multi-Indication Target. If the CSC agrees on the appropriate classification for such Multi-Indication Target, the provisions of clauses (b)-(e) of APPENDIX 3 will apply with respect to such Multi-Indication Target. If the CSC cannot unanimously agree on the appropriate classification for a Multi-Indication Target at the applicable meeting, then such classification will be made pursuant to clause (a) of APPENDIX 3.

(e) ***Neurology Targets that are not High Interest Targets***. Subject to the provisions of Section 1.4 and Section 2.1.1(b) below, during the Research Term, either Party may work outside of the Collaboration on any Neurology Target that is not (i) a High Interest Target for which target validating activities are planned under the then-current Neurological Disease Research Plan, (ii) a Collaboration Target, or (iii) a Biogen Idec Alternate Modality Target.

1.2.4. ***Provision of ASOs for Research Outside of the Neurological Disease Research Program***. During the Research Term, in accordance with and subject to the terms and conditions set forth on SCHEDULE 1.2.4 (which represent the non-financial terms upon which Isis generally

provides its partners on a non-exclusive basis, research ASOs for independent research), Biogen Idec may ask Isis to use its ASO technology to provide research ASOs for up to [***] gene targets each successive [***] month period that are the focus of Biogen Idec programs that are not part of the Collaboration.

1.3. **Process for Designating High Interest Targets as Collaboration Targets or Biogen Idec Alternate Modality Targets**. After the Parties complete the activities to achieve Target Sanction for a particular High Interest Target that is not an ALS Target, Isis will deliver a Target Sanction Data Package for such High Interest Target to the Neurology JRC for review as soon as reasonably practicable. Each time Isis delivers the Neurology JRC a Target Sanction Data Package for a High Interest Target under this Section 1.3 the Parties will schedule a meeting of the Neurology JRC within [***] days following delivery of such Target Sanction Data Package. At such meetings the Neurology JRC will determine and record in the Neurology JRC minutes whether an ASO or Alternate Modality is the best therapeutic approach to pursue for such High Interest Target. If the Neurology JRC cannot unanimously agree on which modality is the best therapeutic approach to pursue for a particular High Interest Target at such meeting, Biogen Idec will have final decision making authority on the matter. Within [***] days following such meeting of the Neurology JRC, by written notice to Isis, Biogen Idec will either designate such High Interest Target as a Collaboration Target (in which case Section 1.6 will apply), a Biogen Idec Alternate Modality Target (in which case Section 1.7 will apply), or a Deferred Target (in which case Section 1.8 will apply). If Biogen Idec does not designate such High Interest Target as a Collaboration Target, a Biogen Idec Alternate Modality Target, or Deferred Target within the timeframe set forth in the previous sentence, then (A) such High Interest Target (I) will not be designated a Collaboration Target or Biogen Idec Alternate Modality Target and (II) will no longer be a Neurology Target under this Agreement and (B) the provisions of Section 2.1.1(f) will apply with respect to such target. Notwithstanding the foregoing, if Isis delivers the Neurology JRC a Target Sanction Data Package for a High Interest Target under this Section 1.3 and such High Interest Target is a Pre-Existing Target, then the Neurology JRC will not meet to discuss which modality is the best therapeutic approach for such High Interest Target, but Biogen Idec will have [***] days after receipt of such Target Sanction Data Package to designate such High Interest Target as a Collaboration Target or a Deferred Target (treating, for purposes of Section 1.8, such target as a High Interest Target for which the

best therapeutic modality was determined to be an ASO) by written notice to Isis, but will not have the right to designate such High Interest Target as a Biogen Idec Alternate Modality Target. If Biogen Idec does not designate such High Interest Target as a Collaboration Target or Deferred Target within the timeframe set forth in the previous sentence, then (X) such High Interest Target (I) will not be designated a Collaboration Target or a Deferred Target and (II) will no longer be a Neurology Target under this Agreement and (Y) the provisions of clause (x) (but not clause (y)) of Section 2.1.1(f) will apply with respect to such target.

1.4. **Process for Designating Isis Neurology Targets as Collaboration Targets**. If, during the Research Term in the course of conducting work outside of the Collaboration with respect to any Isis Neurology Target, Isis achieves Target Sanction with respect to such Isis Neurology Target, then Isis will deliver a Target Sanction Data Package for such Isis Neurology Target to the Neurology JRC for review as soon as reasonably practicable. Within [***] days after the date Isis delivered the applicable Target Sanction Data Package to the Neurology JRC, by written notice to Isis, Biogen Idec will either designate such Isis Neurology Target as a Collaboration Target (in which case Section 1.6 will apply), or, to the extent permitted below, a Biogen Idec Alternate Modality Target (in which case Section 1.7 will apply). If such Isis Neurology Target was not a High Interest Target on the date of Target Sanction, Biogen Idec will only have the right to designate such target as a Collaboration Target (and not, for the avoidance of doubt, as a Biogen Idec Alternate Modality Target). If Biogen Idec does not designate such Isis Neurology Target as a Collaboration Target, or a Biogen Idec Alternate Modality Target within [***] days after the date Isis delivered the applicable Target Sanction Data Package to the Neurology JRC, such Isis Neurology Target will no longer be a Neurology Target under this Agreement and Isis and its Affiliates may work independently or with any Third Party with respect to the discovery, research, development, and commercialization of ASOs (or any other compounds) targeting such Isis Neurology Target.

1.5. **Process for Designating ALS Targets as Collaboration Targets**. If Biogen Idec desires Isis to initiate ASO drug discovery activities on a particular ALS Target, then at the same time the Neurological Disease Research Plan for the Calendar Year in which Biogen Idec desires Isis to initiate such activities is updated to include activities for such Calendar Year, Biogen Idec will designate such ALS Target as a Collaboration Target by providing written notice to Isis; *provided*, if such ALS Target is a Multi-Indication Target, Biogen Idec cannot designate such ALS Target as a Collaboration Target until such target has been classified by the CSC or by operation of APPENDIX 3 as a Primarily Neuro Multi-Indication Target, Equal Multi-Indication Target or Primarily Other Multi-Indication Target. In addition, Biogen Idec cannot designate more than [***] ALS Targets as Collaboration Targets in any successive [***]-month period, and the total number of ALS Targets that are Collaboration Targets cannot exceed [***] without the Parties' mutual agreement.

1.6. **Consequences of Designating Collaboration Targets**.

1.6.1. Subject to and in accordance with the terms of this Agreement, for each Collaboration Target designated under Section 1.3, Section 1.4, Section 1.5,

Section 1.8, Section 3.2.1, or Section 3.2.4.1, Isis and Biogen Idec will be responsible for conducting collaboration programs in accordance with this Agreement to discover, Develop and Manufacture Collaboration Products and, upon Biogen Idec's exercise of the applicable Option, Biogen Idec will be responsible for Commercializing Collaboration Products (each, a "***Collaboration Program***"). For each Collaboration Target, an ASO Development Candidate Identification Plan and Initial Development Plan will be established pursuant to Section 1.10.1 and Section 1.10.2(d), respectively. For each Collaboration Program, Isis will use its Commercially Reasonable Efforts to (i) conduct drug discovery activities, according to the applicable ASO Development Candidate Identification Plan to identify a Development Candidate for the applicable Collaboration Target, and (ii) for each Collaboration Program that is not an ALS Collaboration Program, conduct drug development activities for each Development Candidate through completion of the first PoC Trial in accordance with the applicable Initial Development Plan; *provided that*, in each case unless the Neurology JRC unanimously agrees under Section 1.11 to re-allocate resources to support additional Collaboration Programs, Isis will not be required to commence work on more than [***] Collaboration Programs in any rolling [***] month period; *provided, further that*, if Biogen Idec has designated more than [***] High Interest Targets as Collaboration Targets pursuant to Section 1.3 in any rolling [***] month period, such excess targets will be treated the

same as "*Deferred Targets*" hereunder until the earlier of (a) such time as Isis has agreed to commence work on such excess targets, (b) such time as Isis is otherwise obligated to commence such work hereunder because Isis has commenced work on fewer than [***] targets in a rolling [***] month period and (c) the expiration of the Research Term and, notwithstanding the provisions of Section 6.2.1, Biogen Idec will not be obligated to make the payment under Section 6.2.1 with respect to such target until such time. For each ALS Collaboration Program, Biogen Idec will use its Commercially Reasonable Efforts to conduct drug development activities for each Development Candidate through completion of the [***] in accordance with the applicable Initial Development Plan.

1.6.2. *Notwithstanding the foregoing*, if the applicable Collaboration Target is an Equal Multi-Indication Target, the Parties will not conduct any activities under this Section 1.6 unless and until Isis and Biogen Idec have agreed on a development plan and enhanced economic provisions to be paid by Biogen Idec for the Non-Neurological Indications pursuant to Section (c) of APPENDIX 3.

1.7. **Consequences of Designating Biogen Idec Alternate Modality Targets**. If Biogen Idec designates a particular Neurology Target a Biogen Idec Alternate Modality Target under this Agreement (including Section 1.3, Section 1.4, Section 1.8, Section 3.2.2 or Section 3.2.4.2), Biogen Idec will pay Isis the milestone payment under Section 6.2.2 within [***] days of the designation of such Biogen Idec Alternate Modality Target, *provided, however*, if Biogen Idec determines that an HSR Filing is required to be made under the HSR Act for Biogen Idec to receive the license under Section 4.1.1(b) with respect to such Biogen Idec Alternate Modality Target and notifies Isis of such determination

within five days after the designation of such Biogen Idec Alternate Modality Target, the Parties will promptly file an HSR Filing in accordance with Section 3.1.4 and the due date for Biogen Idec to pay Isis the milestone payment under Section 6.2.2 will be extended until 5:00 pm (Eastern Time) on the [***] Business Day after the HSR Clearance Date.

1.8. **Deferring the Selection of a Collaboration Target or Biogen Idec Alternate Modality Target**.

1.8.1. ***Right to Defer***. If under Section 1.3 Biogen Idec provides Isis a notice (each, a "***Deferral Notice***") electing to defer selecting a High Interest Target as a Collaboration Target or a Biogen Idec Alternate Modality Target (each, a "***Deferred Target***"), and there is at least [***] at the time of Deferral Notice, then Biogen Idec may defer selecting such High Interest Target as a Collaboration Target or a Biogen Idec Alternate Modality Target for a period of up to the shorter of (i) (A) with respect to any High Interest Target for which the best therapeutic modality was determined to be an ASO, [***] or (B) with respect to any High Interest Target for which the best therapeutic modality was determined to be an Alternate Modality, [***], or (ii) the end of the Research Term (the "***Deferral Period***"); *provided, however*, Biogen Idec may only defer up to [***] High Interest Targets under this Section 1.8.1 at any given time. For the avoidance of doubt, the limitation in the preceding proviso will not apply with respect to any Collaboration Target that is treated the same as a Deferred Target pursuant to Section 1.6.1.

1.8.2. ***Deferral Fee***. For each High Interest Target Biogen Idec elects to defer under this Section 1.8, Biogen Idec will pay Isis an annual deferral fee of (a) $[***] for each such Deferred Target for which the best therapeutic approach is determined to be an ASO or (b) $[***] for each such Deferred Target for which the best therapeutic approach is determined to be an Alternate Modality, in each case, in accordance with Section 1.3. No deferral fee will be due under this Section 1.8.2 with respect to any Collaboration Target that is treated the same as a Deferred Target pursuant to Section 1.6.1. Each annual deferral fee for a Deferred Target will be paid in advance for the ensuing [***] month period, with the initial annual deferral fee for all Deferred Targets due within [***] days after the date Biogen Idec delivers the applicable Deferral Notice to Isis, and each annual deferral fee due thereafter during the Deferral Period on the anniversary of the date Biogen Idec delivered such Deferral Notice. If any such annual deferral fee is due after the date that is [***] year prior to the expiration of the Research Term, such deferral fee will be pro-rated to account for the number of days remaining in the Research Term (where such pro-ration will be based on the number of days between the due date for such deferral fee and the end of the Research Term, divided by 365).

1.8.3. ***Designating a Deferred Target as a Collaboration Target or Biogen Idec Alternate Modality Target; Credit for Deferral Fees***. Biogen Idec may designate a Deferred Target as a Collaboration Target or Biogen Idec Alternate Modality Target, as applicable, by delivering written notice to Isis of such designation (and

if a Biogen Idec Alternate Modality Target, the milestone payment under Section 6.2.2), before the expiration of the applicable Deferral Period under this Section 1.8; *provided*, *however*, that Biogen Idec will not be permitted to designate such Deferred Target as a Biogen Idec Alternate Modality Target if such Deferred Target is a Pre-Existing Target. Biogen Idec may credit [***]% of the total amount paid to Isis under Section 1.8.2 for such Deferred Target against the milestone payment under Section 6.2.1 or Section 6.2.2, as applicable, for such Deferred Target. If Biogen Idec does not designate a Deferred Target as a Collaboration Target or Biogen Idec Alternate Modality Target in accordance with this Section 1.8.3 before the expiration of the applicable Deferral Period, then such gene target will no longer be a Neurology Target under this Agreement and any payments made by Biogen Idec under this Section 1.8 for such Deferred Target will be non-creditable and non-refundable.

1.8.4. **Accelerating the Deferral Period with a Deferred Target Development Candidate**.

(a) Isis and its Affiliates may, for its own benefit and not for the benefit of any Third Party, conduct drug discovery activities to identify a Development Candidate for any Deferred Target for which the best therapeutic modality was determined to be an ASO (such Development Candidate, a "***Deferred Target Development Candidate***"); *provided* that Isis may not use the FTEs provided for under Section 1.11 to conduct such activities. Isis will notify the Neurology JRC of any such activities and keep the Neurology JRC reasonably apprised of the status thereof at each meeting of the Neurology JRC. If Isis designates a Deferred Target Development Candidate targeting a particular Deferred Target (such target, an "***Accelerated Target***"), Isis may notify Biogen Idec in writing regarding Isis' designation of such Deferred Target Development Candidate and will provide Biogen Idec the applicable Development Candidate Data Package. Within [***] days following Biogen Idec's receipt of the applicable Development Candidate Data Package, Biogen Idec may designate the Accelerated Target as a Collaboration Target; *provided*

however, that if Biogen Idec designates such Accelerated Target as a Collaboration Target, in addition to any credits for annual deferral fees under Section 1.8.3, Biogen Idec may credit a pro-rated portion of the un-credited [***]% of the last annual deferral fee paid to Isis under Section 1.8.2 for such Deferred Target towards the applicable milestone payment under Section 6.2.1 (where such pro-ration will be based on the number of days between the payment of such deferral fee and the applicable designation of such Accelerated Target as a Collaboration Target, divided by the lesser of 365 days and the number of days between the payment of such deferral fee and the end of the Research Term).

(b) If Biogen Idec does not, within such 90 day period, designate the Accelerated Target as a Collaboration Target under this Section 1.8.4, then, such Accelerated Target will no longer be a Neurology Target and Isis and its Affiliates may work independently or with any Third Party with respect to the discovery, research, development, and commercialization of ASOs (or any other compounds) targeting such Accelerated Target; *provided however* that if prior to the end of the Deferral Period originally applicable to such Accelerated Target, Isis or any of its Affiliates enters into an agreement with a Third Party pursuant to which Isis or its Affiliate grants such Third Party a license to develop or commercialize such Deferred Target Development Candidate, Isis will pay to Biogen Idec [***]% of any amounts (other than Excluded Payments) received by Isis or its Affiliate under such agreement with such Third Party until such time as Isis has reimbursed Biogen Idec for [***]% of the last annual deferral fee paid to Isis under Section 1.8.2 for such Deferred Target.

1.9. **End of Research Term**. At the end of the Research Term, (i) neither Isis nor Biogen Idec will have an obligation to perform any activities under the Core Research Program or the Neurological Disease Research Program; (ii) the High Interest Target List (including the ALS Targets) will be dissolved, and any Neurology Targets that have not been designated Collaboration Targets or Biogen Idec Alternate Modality Targets will no longer be Neurology Targets under this Agreement; (iii) Isis' obligations and Biogen Idec's rights under this Agreement with respect to such Neurology Targets and any ASOs targeting such Neurology Targets will then terminate; and (iv) at Isis' request, Biogen Idec will provide to Isis any data generated under the Core Research Program and the Neurological Disease Research Program and licensed to Isis under Section 4.3.2. For clarity, the expiration of the Research Term will not affect Biogen Idec's rights or Isis' obligations with respect to Collaboration Programs or Biogen Idec Alternate Modality Programs under this Agreement, including, in the case of Collaboration Programs, Isis' obligation under Section 1.10.1 to use Commercially Reasonable Efforts to identify a Development Candidate for each applicable Collaboration Program.

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

1.10.1. **Development Candidate Identification**.

(a) **ASO Development Candidate Identification Plans**. For each Collaboration Program, within [***] days after the designation of the applicable Collaboration Target, Isis will provide the Neurology JRC an initial draft plan to identify a Development Candidate under the applicable Collaboration Program, (such plan, as may be modified from time to time to address the discovery, research and optimization activities Isis will conduct under the applicable Collaboration Program an "***ASO Development Candidate Identification Plan***"). The Neurology JRC will review such plan and agree on a final ASO Development Candidate Identification Plan for such Collaboration Program, which

plan will be generally consistent with Isis' other plans for other gene targets. Isis will carry out its drug discovery efforts for each Collaboration Program pursuant to the applicable ASO Development Candidate Identification Plan in a manner consistent with its internal practices for other gene targets with the goal of identifying a Development Candidate for the applicable Collaboration Program as soon as practicable; *provided* Isis will not start work on any Equal Multi-Indication Target unless and until Isis and Biogen Idec have agreed on a development plan and enhanced economic provisions to be paid by Biogen Idec for Non-Neurological Indications in accordance with APPENDIX 3. Isis will update each ASO Development Candidate Identification Plan as needed and submit it to the Neurology JRC for its review and approval. For each Collaboration Program, Biogen Idec will pay Isis the milestone payment set forth in Section 6.2.1 following receipt of the applicable Design Notice.

(b) **ASO Development Candidate Identification Term**. On a Collaboration Program-by-Collaboration Program basis, the term for the conduct of the applicable ASO Development Candidate Identification Plan (the "***ASO Development Candidate Identification Term***") will begin on the date the applicable Neurology Target becomes a Collaboration Target and will end upon the earlier of (i) designation of a Development Candidate for such Collaboration Program and (ii) the date on which Isis notifies Biogen Idec that, Isis has in good faith determined that the identification of a Development Candidate under the applicable ASO Development Candidate Identification Plan is no longer technically feasible under the then-current state of the art (a "***Technical Failure***"). If Biogen Idec disagrees with Isis' determination that a Technical Failure has occurred, it may refer the matter to an independent qualified Third Party expert accepted by both Parties for final resolution of the dispute. The expert will use the information, materials and data provided to her or him by either Party to promptly resolve the dispute. The decision of the expert will be binding upon both Parties. [***] the costs of the expert. Should the Parties fail to agree on the expert within [***] days following either Party's request to nominate an expert under this Section 1.10.1(b), each Party will nominate an independent expert (who will not be a current or former employee of a Party or any of their Affiliates or have any personal or financial interest in a Party or any of their Affiliates), and promptly thereafter, those two independent experts will agree on the Third Party expert to resolve the dispute in accordance with this Section 1.10.1(b). In the event of any expert proceeding under this Section 1.10.1(b), Isis will not be required to conduct the applicable ASO Development Candidate Identification Plan during the pendency of such proceeding. The Parties anticipate that the last ASO Development Candidate Identification Term will end approximately [***] years after the Effective Date.

(c) **End of ASO Development Candidate Identification Term**. At the end of the ASO Development Candidate Identification Term for a particular Collaboration Program that did not reach the Development Candidate stage, subject to Section 1.10.1(d), (i) neither Isis nor Biogen Idec will have an obligation to perform any activities under this Section 1.10 with respect to such Collaboration Program; (ii) such program will no longer be a Collaboration Program and the applicable gene target associated therewith will no longer be a Collaboration Target; (iii) Isis' obligations and Biogen Idec's rights under this Agreement with respect to the gene targets and any ASOs targeting such gene targets under such Collaboration Program will then terminate; and (iv) upon Isis' request, Biogen Idec will provide to Isis any data generated under the Collaboration Program and licensed to Isis under Section 4.3.2. For clarity, with respect to each Development Candidate that has reached the Development Candidate stage by the end of the ASO Development Candidate Identification Term, the expiration of the ASO Development Candidate Identification Term will not affect Isis' obligation under Section 1.10.3 and Section 1.10.4 to Develop each such Development Candidate through the completion of the first PoC Trial.

(d) **Carryover Development Candidates**. If, by the end of the ASO Development Candidate Identification Term for a particular Collaboration Program, Isis has not designated a Development Candidate for such Collaboration Program, and at any time during the [***] period after the end of the applicable ASO Development Candidate Identification Term Isis' RMC designates an ASO discovered by Isis that is designed to bind to the RNA that encodes the Collaboration Target for such Collaboration Program as a development candidate ready to start IND-Enabling Toxicology Studies (such ASO, a "***Carryover Development Candidate***"), then, Isis will notify Biogen Idec and will provide Biogen Idec with the data package presented to Isis' RMC to approve such Carryover Development Candidate. Biogen Idec will then have [***] days from its receipt of such package to elect to enter into an amendment to this Agreement under the same terms as set forth in this Agreement (except that no additional upfront payment under Section 6.1 will be due). If, within [***] days 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 Carryover Development Candidate, the Parties will execute an amendment to this Agreement regarding such Carryover Development Candidate on such terms. Otherwise, Isis will have no further obligations and Biogen Idec will have no further rights with respect to such Carryover Development Candidate.

1.10.2. Development Candidates; Initial Development Plans; Option Acceleration.

(a) **Appointment of JDC.** For each Development Candidate, the CSC will appoint a Neurology JDC approximately [***] days prior to the date Isis expects to designate a Development Candidate. Such Neurology JDC can be either a new or existing Neurology JDC, but at least one of each Party's Neurology JDC members must have the relevant disease area expertise for the particular Development Candidate.

(b) **Development Candidate Data Package**. For each Collaboration Program, Isis will notify the applicable Neurology JDC in writing within [***] days after designating a Development Candidate and will provide such Neurology JDC the applicable Development Candidate Data Package.

(c) **IND-Enabling Toxicology Studies**.

(i) For each Development Candidate under a Collaboration Program that is not an ALS Collaboration Program, the applicable Neurology JDC will agree upon a high level pre-clinical toxicology strategy no later than [***] days following its receipt of the applicable Development Candidate Data Package. Isis will conduct the IND-Enabling Toxicology Studies under such strategy to the extent consistent with the activities set forth on SCHEDULE 1.10.2(C); *provided, however*, if the initial strategy or applicable Initial Development Plan requires IND-Enabling Toxicology Studies that are in addition to or different from the activities set forth on SCHEDULE 1.10.2(C), then Biogen Idec will pay Isis the costs of such additional or different activities to the extent such costs exceed [***]% of the costs of the activities set forth on SCHEDULE 1.10.2(C). Such additional costs will be Biogen Idec-Approved Costs and will be handled in accordance with the process described in Section 1.14.

(ii) For each ALS Collaboration Program, the applicable Neurology JDC will agree upon a high level pre-clinical toxicology strategy. In addition, the applicable Neurology JDC will approve any study protocols for the IND-Enabling Toxicology Studies. If the Neurology JDC is unable to agree on such high level pre-clinical toxicology strategy or study protocols for a particular ALS Collaboration Program, the matter will be referred to the CSC for resolution. If the CSC cannot agree on such a high level pre-clinical toxicology strategy or study protocol (as applicable) within [***] days after the matter is so referred, Biogen Idec will have final decision-making authority with respect thereto for IND-Enabling Toxicology Studies conducted by Biogen Idec. Solely with respect to the first ALS Collaboration Program to have a Development Candidate, Isis will conduct the IND-Enabling Toxicology Studies utilizing the same mechanics as set forth in

Section 1.10.2(c)(i), and upon Initiation of such IND-Enabling Toxicology Studies Biogen Idec will pay Isis the applicable milestone payment under Section 6.5. Biogen Idec will conduct, [***], all other IND-Enabling Toxicology Studies for the ALS Collaboration Programs. If, with respect to a particular ALS Collaboration Program, Biogen Idec desires Isis to provide consulting or advisory services, and Isis agrees to perform such services, Biogen Idec will pay the costs of performing such services using the payment mechanisms set forth in Section 1.14.

(d) **Initial Development Plans**. For each Development Candidate under a Collaboration Program within [***] after designation of such Development Candidate, the applicable Neurology JDC will agree on an appropriate clinical development plan for such Development Candidate through completion of the first PoC Trial (each, an "***Initial Development Plan***"). If the Neurology JDC cannot agree upon the Initial Development Plan for a particular Collaboration Program, the matter will be referred to the CSC for resolution. If the CSC cannot agree on the Initial Development Plan within [***] days after the matter is so referred, [***] will have final decision-making authority with respect to the contents of the Initial Development Plan.

(i) The Party responsible for conducting the Clinical Studies under a Collaboration Program will file and maintain the IND and other communications with Regulatory Authorities for each Collaboration Program consistent with Section 5.2.1.

(ii) If the requirements of the Phase 1 Trial Design for a Collaboration Program that is not an ALS Collaboration Program require (i) more than [***] human subjects, including single ascending dose and multiple ascending dose arms, or (ii) dosing longer than [***], then Isis may elect to either (1) conduct such larger or longer Phase 1 Trial (in which case Section 1.10.2(e) will apply), or (2) have Biogen Idec conduct such Phase 1 Trial. If Isis elects to have Biogen Idec conduct such Phase 1 Trial, then Biogen Idec will conduct the Phase 1 Trial with Isis' reasonable cooperation and in lieu of the applicable milestone payment payable to Isis pursuant to Section 6.4 (as calculated in accordance with Section 1.10.2(e)) with respect to such Phase 1 Trial, Biogen Idec will pay Isis a milestone payment equal to $[***].

(iii) If the Initial Development Plan relates to an ALS Collaboration Program, then Biogen Idec will conduct the Phase 1 Trial and will pay Isis a milestone payment in the amount as set forth in TABLE 2 of Section 6.5.

(iv) Based on such Initial Development Plan, the CSC will update SCHEDULE 5.1.4 to add Specific Performance Milestone Events related to Biogen Idec's Development and Commercialization of the Development Candidate following Option exercise, which Specific Performance Milestone Events will be generally consistent with Biogen Idec's development timelines for its other drug development programs of similar stage and market potential. If the CSC cannot unanimously agree upon the Specific Performance Milestone Events for a particular Collaboration Program within [***] days after the date the CSC started discussing such Specific Performance Milestone Events, the matter will be referred to expert resolution pursuant to Section 12.1.4. Isis will update each Initial Development Plan as needed, but at least once Annually, and submit it to the applicable Neurology JDC for its review and approval. If the applicable Neurology JDC cannot agree on the contents of any updated Initial Development Plan, the matter will be resolved in accordance with the procedures for establishing the Initial Development Plan set forth in this Section 1.10.2(d).

(e) **Cost Estimates**. Within [***] after designation of a Development Candidate under a Collaboration Program that is not an ALS Collaboration Program, the applicable Neurology JDC will agree on the expected cost for Isis to conduct the work (other than the IND-Enabling Toxicology Study) specified in the applicable Initial Development Plan, including Isis' expected [***] and [***] costs (each, a "***Cost Estimate***"). Based on the Cost Estimates, the Neurology JDC will establish the [***] and [***] milestone payments for such Collaboration Program, which payments will be equal to (i) [***]; plus (ii) [***] and recommend such milestone payments to the CSC for approval. The Parties will negotiate in good faith using the Isis/Biogen Idec Preexisting Development Agreements as a basis for costs estimates. As part of this process, Isis will provide the Neurology JDC with a good faith estimate of the cost to conduct the work necessary to develop such Development Candidates under the applicable Initial Development Plan using a similar methodology as used under the Isis/Biogen Idec Preexisting Development Agreements. If the Neurology JDC cannot agree on the Cost Estimates, the matter will be referred to the CSC for resolution.

(f) **Obligation to Start Development Activities**. Isis will not be required to conduct any Development activities for a Development Candidate if the Initial Development Plan, Specific Performance Milestone Events and the corresponding Cost Estimates have not been agreed to pursuant to this Section 1.10.2.

(g) **Option Acceleration**. If the PoC Trial for a Collaboration Program that is not an ALS Collaboration Program will be [***] or more, or require more than [***], then, if Isis provides to Biogen Idec the notice described in the following sentence, Isis will not be required to conduct such PoC Trial for such Collaboration Program. Isis will notify Biogen Idec within [***] after finalization of the initial PoC Trial Design pursuant to Section 1.10.2(d) (or each time there is a material change thereto) for a Collaboration Program that is not an ALS Collaboration Program if Isis elects not to conduct such PoC Trial for such Collaboration Program (such notice, an "***Option Acceleration Notice***"). If Isis has delivered an Option Acceleration Notice as provided in this Section 1.10.2(g), Biogen Idec will have [***] from its receipt of the data generated under the [***] for the first Phase 1 Trial for such Collaboration Program (an "***Option Acceleration Deadline***") to exercise its Option for the applicable Collaboration Program. If Biogen Idec does not exercise its Option for the applicable Collaboration Program by the applicable Option Acceleration Deadline, Biogen Idec's Option under Section 3.1 with respect to such Collaboration Program will expire and such Collaboration Program will terminate.

After Biogen Idec's receipt of an Option Acceleration Notice with respect to a particular Collaboration Program, the Parties will mutually agree on the contents of all correspondence with and submissions to Regulatory Authorities to the extent related to the PoC Trial for the applicable Collaboration Program; *provided, however*, that if the Parties cannot so mutually agree, then [***] will have final decision-making authority but will not deliver any correspondence to Regulatory Authorities related to the PoC Trial for the applicable Collaboration Program that is not mutually agreed by the Parties unless [***] determines such correspondence is required to be delivered and cannot be delayed.

(h) **Attaching Plans to Neurology JDC Minutes**. The Neurology JDC will attach each Initial Development Plan and, if applicable, associated Cost Estimates to the minutes of the Neurology JDC for the meeting at which such Initial Development Plan and, if

applicable, Cost Estimates were agreed. For clarity, such Initial Development Plan and Cost Estimates need not be agreed to at the same meeting of the Neurology JDC.

1.10.3. **Development Term**. The term for the conduct of the Drug Development Program will begin on the designation of the first Development Candidate and will end upon the earlier of (i) completion of the Initial Development Plans under all Collaboration Programs, which the Parties estimate will be approximately [***] years after the Effective Date, (ii) exercise by Biogen Idec of its Option for all Collaboration Programs; (iii) the termination of the last Collaboration Program;

and (iv) mutual agreement of the Parties to terminate the Drug Development Program.

1.10.4. **Drug Development**.

(a) ***Non-ALS Collaboration Programs*.** For each Collaboration Program that is not an ALS Collaboration Program, Isis will use Commercially Reasonable Efforts to conduct all activities under each Initial Development Plan on the timeline set forth in the applicable Initial Development Plan. Without limiting the foregoing, Isis may discontinue Development under an Initial Development Plan if after having consulted, and having given good faith consideration to the recommendations of the Neurology JDC 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 under an Initial Development Plan, Isis will provide Biogen Idec with reasonable advance notice of such discontinuation, including the grounds for Isis' determination. If Isis elects to discontinue Development under an Initial Development Plan pursuant to this Section 1.10.4(a), Biogen Idec may, in its discretion, elect to continue Development of the applicable Development Candidate by providing Isis with written notice of Biogen Idec's exercise of the Option within [***] after Isis' written notice to Biogen Idec of such discontinuation and [***]. If Biogen Idec does not timely exercise its Option under this Section 1.10.4(a), then the Option will expire.

(b) ***Phase 1 Trials***. Each Phase 1 Trial will be conducted in accordance with the applicable Phase 1 Trial Design set forth in the applicable Initial Development Plan.

(i) At meetings of the applicable Neurology JDC Isis will keep Biogen Idec informed of the progress and status of each Phase 1 Trial conducted by Isis. When Isis [***] a Phase 1 Trial, Isis will notify Biogen Idec in writing of such measurement within [***] days of the conclusion of such Phase 1 Trial. Isis will provide Biogen Idec with the data generated under the [***] for such Phase 1 Trial as soon as practicable after such notice.

(ii) If, in accordance with Section 1.10.2(d) or under an ALS Collaboration Program, Biogen Idec conducts a Phase 1 Trial for a Collaboration Program, at meetings of the applicable Neurology JDC Biogen Idec will keep Isis informed of the progress and status of such Phase 1 Trial. When Biogen Idec [***] a Phase 1 Trial, Biogen Idec will notify Isis in writing of such [***] within [***] days of the conclusion of such Phase 1 Trial. Biogen Idec will

provide Isis with the data generated under the [***] for such Phase 1 Trial as soon as practicable after such notice.

(c) ***PoC Trial***. Each PoC Trial will be conducted in accordance with the PoC Trial Design set forth in the applicable Initial Development Plan.

(i) At meetings of the applicable Neurology JDC, Isis will keep Biogen Idec informed of the progress and status of each PoC Trial conducted by Isis. When Isis [***] a PoC Trial under the applicable Initial Development Plan, Isis will notify Biogen Idec in writing within [***] days after such measurement. Isis will provide Biogen Idec with the [***] as soon as practicable after such notice.

(ii) If Biogen Idec exercises its Option prior to the Initiation of the first PoC Trial for a Collaboration Program or if Biogen Idec conducts the first PoC Trial for an ALS Collaboration Program, then at meetings of the applicable Neurology JDC Biogen Idec will keep Isis informed of the progress and status of the PoC Trial for such Collaboration Program. When Biogen Idec completes such PoC Trial, Biogen Idec will notify Isis in writing within [***] days after such completion, and will provide Isis with [***] as soon as practicable after such notice.

1.10.5. **Briefing the Neurology JRC, Neurology JDC and CSC; Conduct of Research and Development**. At each regularly scheduled meeting of the Neurology JRC, the Parties will provide progress updates on (i) the Neurological Disease Research Program and progress toward achieving Target Sanction for each High Interest Target and progress related to ALS Targets; (ii) activities conducted under the Core Research Program; (iii) progress under each ASO Development Candidate Identification Plan toward designating a Development Candidate; (iv) activities on the Deferred Targets conducted pursuant to Section 1.8.4, and (v) the progress of any Isis Neurology Targets (including the estimated time for each Isis Neurology Target to achieve Target Sanction), in each case, together with a summary of data associated with each Party's research and/or Development activities for each Collaboration Program. At each Neurology JDC meeting, the Parties will provide progress updates on activities conducted under the Initial Development Plans for the applicable Development Candidates, together with a summary of data associated with each Party's Development activities for the applicable Collaboration Program. At each CSC meeting, the Parties will provide any information reasonably requested by the members of the CSC in advance of such meeting.

1.10.6. **Clinical Supplies by Isis**. For Collaboration Programs that are not ALS Collaboration Programs, Isis, at its expense, will supply API (on its own or through a CMO approved by Biogen Idec) and Clinical Supplies to support the Research and Development activities under each

Neurology Plan through Option Exercise. If Biogen Idec exercises an Option for a Collaboration Program that is

not an ALS Collaboration Program at least [***] prior to the planned Initiation of the PoC Trial for the applicable Collaboration Program, Biogen Idec may elect to either have (a) Isis supply Clinical Supplies for such PoC Trial (on its own or through a CMO approved by Biogen Idec), in which case Biogen Idec will pay Isis an amount equal to [***], or (b) a CMO supply Clinical Supplies for such PoC Trial in accordance with the Manufacturing Agreement entered into with such CMO. If Biogen Idec exercises an Option for a Collaboration Program that is not an ALS Collaboration Program prior to, but less than [***] before, the planned Initiation of the PoC Trial for the applicable Collaboration Program, Isis will supply Clinical Supplies for such PoC Trial (on its own or through a CMO approved by Biogen Idec) and Biogen Idec will pay Isis an amount equal to [***]. For ALS Collaboration Programs, Isis will supply API (on its own or through a CMO approved by Biogen Idec) and Clinical Supplies to support the Research and Development activities under each Neurology Plan through the first Phase 2 Trial, and such supply will be at Biogen Idec's expense using the mechanism set forth in Section 1.14.

1.10.7. **Collaborations with Academics and Non-Profit Institutions**. Each Party (the "***Contracting Party***") may engage one or more academic or non-profit institutions to conduct work under any Neurology Plan or on any High Interest Target, Collaboration Target or Deferred Target, *provided however* that, with respect to any such academic or non-profit institution engaged to conduct such activities with respect to a High Interest Target, Collaboration Target or Deferred Target where such engagement begins after the date such High Interest Target, Collaboration Target or Deferred Target is designated, (i) the other Party may provide the Contracting Party comments on the proposed terms of any agreement or amendment to an existing agreement to be entered into with such institution, and (ii) so long as the other Party provides the Contracting Party such comments within [***] days of receiving a draft of such agreement from the Contracting Party, the Contracting Party will [***]. The Contracting Party will not be responsible for [***] as a result of the other Party's [***] to the terms of any agreement with any such academic or non-profit institution.

1.11. **Resource Allocations**. During the first [***] following the Effective Date, Isis will use Commercially Reasonable Efforts to build a team of [***] FTEs to perform the activities under the Core Research Plan, the Neurological Disease Research Plan, and the target validation activities contemplated under SCHEDULE 1.2.4; and thereafter until the sixth anniversary of the Effective Date, Isis will dedicate [***] FTEs to perform such activities; *provided*, Isis may utilize [***] of such [***] FTEs to perform drug discovery activities on ALS Targets as agreed by the Neurology JRC. At all times during such period, such FTEs will have experience and qualifications similar to that of the FTEs initially assigned to perform such activities hereunder. Biogen Idec will be responsible for devoting its resources toward specific research efforts under the Core Research Program and Neurological Disease Research Program as reasonably determined by Biogen Idec. During the [***] after the Effective Date, [***] of Isis' [***] FTEs will be allocated to activities focused on Core Technology Research and the Neurology JRC will

determine the appropriate allocation of resources thereafter. Isis will update the Neurology JRC at each meeting thereof on the utilization of such FTEs and provide the Neurology JRC with summaries of resource and FTE utilization in a format mutually agreed to by each Party's Alliance Managers. Biogen Idec may also choose to supplement Isis' efforts under the Core Research Plan and the Neurological Disease Research Plan with its own scientists at various points throughout the Research Term. After the sixth anniversary of the Effective Date, Isis will provide sufficient resources to perform its obligations under each Collaboration Program as reasonably determined by Isis.

1.12. **Research and Development Costs Paid by Isis.**

1.12.1. **Research Programs**. During the Research Term, Isis will be responsible for all Isis Activities under the Core Research Program and the Neurological Disease Research Program, and all costs and expenses associated therewith.

1.12.2. **Collaboration Programs**. During the Option Period, on a Collaboration Program-by-Collaboration Program basis, Isis will be responsible for all Isis Activities under the ASO Development Candidate Identification Plan and the Initial Development Plan and, except as otherwise provided under Section 1.13.1, all costs and expenses associated therewith.

1.13. **Research and Development Costs Paid by Biogen Idec.**

1.13.1. **Before Option Exercise.**

(a) **Research Programs**. During the Research Term, Biogen Idec will be responsible for all Biogen Idec Activities under the Core Research Program and Neurological Disease Research Program, and all costs and expenses associated therewith.

(b) **Collaboration Programs**. During the Option Period, on a Collaboration Program-by-Collaboration Program basis, Biogen Idec will be responsible for any Biogen Idec Activities under the ASO Development Candidate Identification Plan and the Initial Development Plan and all costs and expenses associated therewith. In addition, Biogen Idec will be responsible for paying any Biogen Idec-Approved Costs resulting from Biogen Idec-Approved Changes using the payment mechanisms set forth in Section 1.14.

(c) **Additional Activities Approved by Biogen Idec**. If, with respect to a particular Collaboration Program, Biogen Idec desires that either Isis or a Third Party [***] or conduct other work to support Approval of a Collaboration Product, including [***], prior to Option exercise, and Isis agrees to perform such work, Biogen Idec will pay the costs of conducting such work using the payment mechanisms set forth in Section 1.14.

1.13.2. **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 Collaboration Products, including any work performed by Isis at Biogen Idec's request, and all supply chain planning and decision-making.

1.14. **Payment Mechanics for Additional Activities Approved by Biogen Idec**. Biogen Idec will pay Isis (1) costs resulting from requests from Biogen Idec that Isis perform additional work under this Agreement, including, the cost of Isis' time incurred in performing such work at the then-applicable Isis FTE Rate (***"FTE Costs"***), the cost of [***], and any [***] incurred by Isis in performing such work, or (2) Additional Plan Costs resulting from Biogen Idec-Approved Changes (such costs, collectively ***"Biogen Idec-Approved Costs"***). Isis will permit Biogen Idec to review, negotiate (with Isis) and approve all Biogen Idec-Approved Costs; *provided* Biogen Idec will provide a substantive, good faith response within [***] days of Isis' request for approval. For clarity this Section 1.14 does not apply to any Pre-Licensing Milestone payments established under Section 1.10.2(e), and expenses paid under Section 1.14.1 and Section 1.14.2 are not subject to reconciliation.

1.14.1. For Biogen Idec-Approved Costs resulting from [***], Biogen Idec will pay Isis for such Biogen Idec-Approved Costs [***] within [***] days after receipt of the applicable invoice by Biogen Idec following [***].

1.14.2. For Biogen Idec-Approved Costs resulting from [***], Biogen Idec will pay Isis, in accordance with any applicable [***] entered into by the Parties after the Effective Date, for [***]% of such Biogen Idec-Approved Costs within [***] days after receipt of the applicable invoice by Biogen Idec following Biogen Idec's request or approval for such [***], and the remaining [***]% within [***] days after receipt of the applicable invoice by Biogen Idec following [***].

1.14.3. For any Biogen Idec-Approved Cost that has an Estimated Biogen Idec-Approved Cost of less than $[***] and does not result from [***] or from [***], Isis will invoice Biogen Idec directly for such Biogen Idec-Approved Cost in advance, on a [***] Basis based upon the applicable Estimated Biogen Idec-Approved Costs and Biogen Idec will pay the invoices submitted pursuant to this Section 1.14.3 for such Biogen Idec-Approved Costs within [***] days after receipt of the applicable invoice by Biogen Idec. For purposes of this Section 1.14.3, ***"Measurement Period"*** means each [***].

1.14.4. For any Biogen Idec-Approved Costs that has an Estimated Biogen Idec-Approved Cost of $[***] or more and does not result from [***] or [***], Isis will invoice Biogen Idec directly for such Biogen Idec-Approved Cost in advance on a [***] Basis based upon the applicable Estimated Biogen Idec-Approved Costs and Biogen Idec will pay the invoices submitted pursuant to this Section 1.14.4 for such Biogen Idec-Approved Costs within [***] days after receipt of the applicable invoice by Biogen Idec. For purposes of this Section 1.14.4, ***"Measurement Period"*** means each [***].

1.14.5. Within [***] days after the end of the applicable Measurement Period, Isis will provide Biogen Idec with a written statement (1) reconciling the [***] the Estimated Biogen Idec-Approved Costs and the [***] within the Biogen Idec-Approved Costs (the "***Actual Biogen Idec-Approved Costs***") incurred by Isis during the just-ended Measurement Period and (2) confirming that the FTE Costs portion of the Estimated Biogen Idec-Approved Costs is a reasonable approximation of the actual FTE Costs incurred by Isis during the just-ended Measurement Period. If the Estimated Biogen Idec-Approved Costs exceed the Actual Biogen Idec-Approved Costs for such period, Isis will, offset all such excess payments against any future invoices under this Agreement until Biogen Idec has recouped all such overpayments. If the Estimated Biogen Idec-Approved Costs are less than the Actual Biogen Idec-Approved Costs for such period, Isis will invoice Biogen Idec for the remaining amounts owed to Isis, and Biogen Idec will pay such invoices within [***] days of receipt of such invoice. 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.

1.15. **Participation in Regulatory Meetings**. During the Option Period for each Collaboration Program, each Party will conduct its interactions and communications with Regulatory Authorities in accordance with Section 5.2.

1.16. **Impact of [***] Development Path**. If the Parties mutually agree to amend an Initial Development Plan for a Collaboration Program that is not an ALS Collaboration Program, 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 [***]. Nothing in this Section 1.16 will affect either Party's rights or obligations under Section 1.10.2(g).

1.17. **Research and Development Management**.

1.17.1. **Collaboration Steering Committee**. The Parties will establish a Collaboration steering committee ("***CSC***") with the powers, roles and responsibilities set forth on SCHEDULE 1.17.1 and in this Section 1.17.1 to oversee the Collaboration. The CSC will consist of up to three representatives appointed by Isis and up to three representatives appointed by Biogen Idec. The Neurology JRC and Neurology JDC under this Agreement will report to the CSC. The CSC will determine the CSC operating procedures at its first meeting, including the CSC's policies for replacement of CSC members, policies for participation by additional representatives or consultants invited to attend CSC meetings, and the location of meetings, which will be codified in the written minutes of the first CSC meeting. Each Party will be responsible for the costs and expenses of its own employees or consultants attending CSC meetings. Any decision that may be made by the Neurology JRC or Neurology JDC may be made by the CSC and such decision by the CSC will have the same effect as if made by the Neurology JRC or the Neurology JDC under this Agreement. The CSC may delegate any of its functions

specified in Section 1.17.1(a) below to a Neurology JDC by agreeing to and codifying such delegation in the minutes of the CSC.

(a) **Role of the CSC**. Without limiting any of the foregoing, subject to Section 1.17.4, the CSC will perform the following functions, some or all of which may be addressed directly at any given CSC meeting:

(i) approving the terms on which Biogen Idec would develop and commercialize a product for a non-Neurological Disease indication associated with a Multi-Indication Target as described in APPENDIX 3;

(ii) determining the primary disease association of a Multi-Indication Target;

(iii) appointing a Neurology JDC for each Development Candidate under this Agreement, whether by creating a new Neurology JDC or assigning an existing Neurology JDC to oversee such Development Candidate;

(iv) establishing the Initial Development Plan in the event of a Neurology JDC dispute as described in Section 1.10.2(d);

(v) establishing the Specific Performance Milestone Events as described in Section 1.10.2(d)(iv);

(vi) approving the [***] and [***] milestone payments or establishing such payments if the Neurology JDC is unable to agree on such payments as described in Section 1.10.2(e);

(vii) reviewing and assessing reports provided by the Neurology JRC and the Neurology JDCs;

(viii) providing input to the JPC as appropriate;

(ix) reviewing and providing input on the CTDs and IDPs as appropriate;

(x) assisting with and participating in the resolution of disputes as contemplated in Section 12.1.1; and

(xi) such other review and advisory responsibilities as may be assigned to the CSC by the Parties pursuant to this Agreement.

1.17.2. **Neurology JRC**. The Parties will establish a joint research committee (the "***Neurology JRC***") reporting to the CSC, to provide advice and make recommendations on the conduct of activities under the Core Research Program, Neurological Disease Research Program and each Collaboration Program up to

Development Candidate designation. The Neurology JRC will consist of up to three representatives appointed by Isis and up to three representatives appointed by Biogen Idec. Each Neurology JRC member will have experience and expertise appropriate for the Core Research Program, Neurological Disease Research Program and/or the stage of development of the Collaboration Programs. Each Party will designate one of its 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 Neurology JRC. The co-chairs will be responsible for overseeing the activities of the Neurology JRC consistent with the responsibilities set forth below in this Section 1.17.2. SCHEDULE 1.17.2 sets forth certain Neurology JRC governance matters agreed to as of the Effective Date. The Neurology JRC will determine the Neurology JRC operating procedures at its first meeting, including the Neurology JRC's policies for replacement of Neurology JRC members, policies for participation by additional representatives or consultants invited to attend Neurology JRC meetings, and the location of meetings, which will be codified in the written minutes of the first Neurology JRC meeting. Each Party will be responsible for the costs and expenses of its own employees or consultants attending Neurology JRC meetings. Isis and Biogen Idec will use reasonable efforts to schedule meetings of the Neurology JRC to take place at the same location and on the same dates as meetings of the CSC and the joint development and steering committees under the Isis/Biogen Idec Preexisting Development Agreements, to maximize the use of each Party's time, increase information sharing efficiencies and reduce the cost of additional travel, lodging and related expenses.

(a) **Role of the Neurology JRC**. Without limiting any of the foregoing, subject to Section 1.17.4, the Neurology JRC will perform the following functions, some or all of which may be addressed directly at any given Neurology JRC meeting:

(i) maintain the list of High Interest Targets, ALS Targets, Collaboration Targets, and Biogen Idec Alternate Modality Targets, as such lists may be updated from time to time in accordance with this Agreement, and attach such lists to the minutes of the meeting of the Neurology JRC where any update to the High Interest Target List, ALS Target List or Collaboration Targets, Biogen Idec Alternate Modality Targets occurred;

(ii) as described in Section 1.2.3(c), determine the number of High Interest Targets for which activities to support Target Sanction will be conducted during each year of the Research Term;

(iii) review and approve amendments to the Core Research Plan and the Neurological Disease Research Plan as described in Sections 1.2.2 and 1.2.3;

(iv) allocate resources under Section 1.11;

(v) as contemplated under Section 1.6.1, determine whether to re-allocate resources on additional Collaboration Programs;

(vi) during years [***] through [***] after the Effective Date, determine the appropriate allocation of Isis' resources to the Core Research Plan, the Neurological Disease Research Plan and each ASO Development Candidate Identification Plan, as described in Section 1.11;

(vii) review the overall progress of Isis' efforts to achieve Target Sanction with respect to each High Interest Target that has not achieved Target Sanction status;

(viii) as described in Section 1.3, review each Target Sanction Data Package and determine the best therapeutic modality to pursue for a High Interest Target;

(ix) as described in Section 1.4, review each Target Sanction Data Package for an Isis Neurology Target;

(x) establish an ASO Development Candidate Identification Plan for each Collaboration Program as described in Section 1.10.1(a);

(xi) as described in Section 1.10.2(c) and Section 1.10.2(d), agree upon a high level pre-clinical toxicology strategy and Initial Development Plan for each Development Candidate;

(xii) review the overall progress of Isis' efforts to discover, identify, optimize and select the Development Candidate for each Collaboration Program;

(xiii) monitoring progress of each Collaboration Program and maintaining a calendar of anticipated milestone achievement dates for each Collaboration Program;

(xiv) establishing teams and committees to oversee and manage activities under the Core Research Program, Neurological Disease Research Program and each Collaboration Program up to Development Candidate designation as it deems necessary;

(xv) discuss upcoming academic and non-profit collaborations that a Party is negotiating or considering entering into; and

(xvi) such other review and advisory responsibilities as may be assigned to the Neurology JRC by the CSC pursuant to this Agreement.

1.17.3. **Joint Development Committees**. For each Development Candidate, the CSC will appoint a joint development committee (each, a "***Neurology JDC***") approximately

[***] days prior to the date Isis expects to designate a Development Candidate, to govern the activities under this Agreement with respect to such Collaboration Program. Each Neurology JDC will report to the CSC and will consist of an equal number of representatives appointed by Isis and Biogen Idec. Each Neurology JDC member will be a senior clinical development leader or have other experience and expertise appropriate for the stage of development of the Collaboration Program in the applicable disease area, and at least one of each Party's members will have operational responsibility for the applicable Collaboration Program. Each Party will designate one of its 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 Neurology JDC. The co-chairs will be responsible for overseeing the activities of the Neurology JDC consistent with the responsibilities set forth below in this Section 1.17.3. SCHEDULE 1.17.3 sets forth certain Neurology JDC governance matters agreed to as of the Effective Date. Each Neurology JDC will determine its operating procedures at its first meeting, including the Neurology JDC's policies for replacement of Neurology JDC members, policies for participation by additional representatives or consultants invited to attend Neurology JDC meetings, and the location of meetings, which will be codified in the written minutes of the first Neurology JDC meeting. Each Party will be responsible for the costs and expenses of its own employees or consultants attending Neurology JDC meetings. If practical, Isis and Biogen Idec will use reasonable efforts to schedule meetings of each Neurology JDC to take place at the same location and on the same dates as meetings of the CSC and the joint development and steering committees under the Isis/Biogen Preexisting Development Agreements, to maximize the use of each Party's time, increase information sharing efficiencies and reduce the cost of additional travel, lodging and related expenses.

(a) **Role of the Neurology JDCs**. Without limiting any of the foregoing, subject to Section 1.17.4, each Neurology JDC will perform the following functions, some or all of which may be addressed directly at any given Neurology JDC meeting:

(i) establish the Initial Development Plan for each Development Candidate and update such plan as needed as provided in Section 1.10.2(d);

(ii) recommend the Cost Estimates to the CSC for approval under Section 1.10.2(e);

(iii) establish a high-level preclinical toxicology strategy for each Collaboration Program under Section 1.10.2(c);

(iv) establishing teams and committees to oversee and manage activities under each Collaboration Program after Development Candidate designation as it deems necessary; and

(v) such other review and advisory responsibilities as may be assigned to the Neurology JDC by the CSC pursuant to this Agreement.

1.17.4. **Decision Making**.

(a) **Committee Decision Making.** Decisions by each of the CSC, Neurology JRC and Neurology JDC will be made by unanimous consent with each Party's representatives having, collectively, one vote. At any given meeting of any such committee, quorum will have deemed to be reached if a voting representative of each Party is present or participating in such meeting. No action taken at any meeting of any such committee will be effective unless there is a quorum at such meeting. Unless otherwise specified in this Agreement, no action will be taken with respect to a matter for which the CSC, Neurology JRC or Neurology JDC, as applicable, has not reached unanimous consensus.

(b) **Implementation.** Each Party will give due consideration to, and consider in good faith, the recommendations and advice of the CSC, the Neurology JRC and Neurology JDC (as applicable) regarding the conduct of the Core Research Program, Neurological Disease Research Program and each Collaboration Program. Subject to Section 1.10.1 and Section 1.10.2, prior to Option exercise, (i) Isis will have the final decision-making authority regarding [***] and (ii) Biogen Idec will have the final decision-making authority regarding [***]. After Option exercise for a particular Collaboration Program, Biogen Idec will have the final decision-making authority regarding [***] of Collaboration Products for such Collaboration Program. Except as otherwise expressly stated in this Agreement, the CSC, the Neurology JRC and Neurology JDC 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.

1.17.5. **Term of the Neurology JRC, Neurology JDC and CSC**. Isis' obligation to participate in (i) the Neurology JRC, will terminate at the end of the ASO Development Candidate Identification Term, (ii) the Neurology JDC, will terminate upon Biogen Idec's exercise (or expiration) of the Option for the last Collaboration Program, and (iii) the CSC, will terminate upon Biogen Idec's exercise (or expiration) of the Option for the last Collaboration Program. Thereafter, for each such governing body, Isis will have the right, but not the obligation, to participate in such meetings upon Isis' request.

1.17.6. **Alliance Managers**. Each Party will appoint a representative to act as its alliance manager under this Agreement (each, an "***Alliance Manager***"). Each Alliance Manager will be responsible for supporting the CSC, the Neurology JRC and Neurology JDC, and performing the activities listed in SCHEDULE 1.17.6.

ARTICLE 2.
EXCLUSIVITY COVENANTS

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

2.1.1. **Exclusivity Covenants**.

(a) **The Parties' Exclusivity Covenants During the Research Term for High Interest Targets**. Each Party agrees that, *except* in the performance of its obligations or exercise of its rights under this Agreement and except as set forth in Section 1.8.4, Section 2.1.2, Section 2.2, Section 10.4.3 or Section 10.4.4, or as contemplated by any Neurology Plan, neither it nor any of its Affiliates will work independently or for or with any Third Party (including the grant of any license to any Third Party) with respect to the discovery, research, development, manufacture or commercialization in the Field of an oligonucleotide that is designed to bind to the RNA that encodes a High Interest Target from the Effective Date until the earlier to occur of (i) the date such target is removed from the High Interest Target List, by Biogen Idec or ceases to be a High Interest Target by operation of this Agreement, or (ii) the date on which the High Interest Target List is dissolved in accordance with Section 1.9.

(b) **Isis' Exclusivity Covenants During the Research Term for Isis Neurology Targets**. Isis agrees that neither it nor any of its Affiliates will work for the benefit of any Third Party (including the grant of any license to any Third Party that would diminish Biogen Idec's rights under Section 1.4 or prevent Isis from granting Biogen Idec a license under Section 4.1.1) with respect to the discovery, research, development, manufacture or commercialization in the Field of an oligonucleotide that is designed to bind to the RNA that encodes an Isis Neurology Target from the Effective Date until the earlier to occur of (i) the date such target ceases to be a Neurology Target by operation of this Agreement, or (ii) the expiration of the Research Term.

(c) **Isis' Exclusivity Covenants for Biogen Idec Alternate Modality Targets**. With respect to each Biogen Idec Alternate Modality Target, *except* in the performance of its obligations or exercise of its rights under this Agreement and except as set forth in Section 2.1.2, Section 10.4.3 or Section 10.4.4, neither Isis nor any of its Affiliates will work independently or for or with any Third Party (including the grant of any license to any Third Party) with respect to the discovery, research, development, manufacture or commercialization of an oligonucleotide designed to bind to the RNA encoding such Biogen Idec Alternate Modality Target without Biogen Idec's prior written consent; *provided, however* that if (A) Biogen Idec, its Affiliates or Sublicensees have not

[***] within [***] (or, if Biogen Idec has used Commercially Reasonable Efforts to [***], within [***]) after the date the applicable Neurology Target becomes a Biogen Idec Alternate Modality Target in accordance with this Agreement, or (B) after [***], Biogen Idec, its Affiliates and Sublicensees thereafter cease to use Commercially Reasonable Efforts to develop or commercialize such Product (or otherwise stops developing or commercializing such Product), then (i) the exclusive license granted to Biogen Idec under Section 4.1.1(b) for such Biogen Idec Alternate Modality Target will convert to a non-exclusive license, and (ii) Isis and its Affiliates may independently or for or with any Third Party (including the grant of any license to any Third Party) research, develop, and commercialize oligonucleotides designed to bind to the RNA encoding such Biogen Idec Alternate Modality Target (each such oligonucleotide, an "***Isis Non-Exclusive Product***"), but not, for the avoidance of doubt, any molecule or product designed to [***] that is not [***], and the license to Biogen Idec under Section 4.1.1(b) will become a non-exclusive license to the extent necessary to allow Isis to conduct such activities.

(d) **The Parties' Exclusivity Covenants During the Option Period for Collaboration Targets**. Each Party agrees that, *except* in the performance of its obligations or exercise of its rights under this Agreement and except as set forth in Section 2.1.2, Section 2.2, Section 10.4.3 or Section 10.4.4, neither it nor any of its Affiliates will work independently or for or with any Third Party (including the grant of any license to any Third Party) with respect to discovery, research, development, manufacture or commercialization in the Field of an oligonucleotide that is designed to bind to the RNA that encodes a Collaboration Target from the date such gene target was designated a Collaboration Target under this Agreement through the expiration or earlier termination of the applicable Option Period.

(e) **The Parties' Exclusivity Covenants After Option Exercise**. *Except* in the performance of its obligations or exercise of its rights under this Agreement and except as set forth in Section 2.1.2, Section 2.2, Section 10.4.3 or Section 10.4.4, if Biogen Idec timely exercises an Option in accordance with this Agreement, then neither Isis nor Biogen Idec nor their respective Affiliates will work independently or for or with any Third Party (including the grant of any license to any Third Party) with respect to:

(i) discovery, research or development in the Field of an oligonucleotide that is designed to bind to the RNA that encodes the applicable Collaboration Target related to such Option until [***]; and

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

(f) **Failure to Defer or Designate a High Interest Target a Collaboration Target or Biogen Idec Alternate Modality Target**. If, after a High Interest Target achieves Target Sanction, Biogen Idec (i) fails to timely designate such High Interest Target as a Collaboration Target or a Biogen Idec Alternate Modality Target (or, if applicable elect to defer under Section 1.3) on the applicable timelines set forth in Section 1.3 or Section 1.8, (ii) fails to timely pay the applicable Milestone Payment under Section 6.2.1 or Section 6.2.2, (iii) under Section 10.2.1 or Section 10.2.2 voluntarily terminates its license under Section 4.1.1(b) with respect to a High Interest Target Biogen Idec designated as a Biogen Idec Alternate Modality Target, or (iv) notifies Isis that it has terminated an ALS Collaboration Program after the Initiation of a Phase 1 Trial for such program or fails to timely pay a milestone payment under Section 6.5 with respect to a particular ALS Collaboration Program, then in each case for a period of [***] after the date of such failure or such termination, as applicable, (x) neither Biogen Idec nor its Affiliates will independently or for or with any Third Party (including the grant of any license to any Third Party) discover, research, develop, manufacture or commercialize an oligonucleotide designed to bind to the RNA encoding such High Interest Target and (y) if Biogen Idec or any of its Affiliates or licensees discovers, researches, develops, manufactures or commercializes a Biogen Idec Alternate Modality Product for such High Interest Target and such High Interest Target is not a Pre-Existing Target, then (A) the provisions of ARTICLE 6 will apply with respect to such Biogen Idec Alternate Modality Product, (B) Biogen Idec will pay Isis all amounts owed (or which would have been owed absent such original failure or such termination) under such ARTICLE 6 with respect to such Biogen Idec Alternate Modality Product (to the extent such amounts have not previously been paid with respect to the applicable Biogen Idec Alternate Modality Target) in accordance with the terms hereof, (C) to the extent Isis has the ability to do so, Isis will grant Biogen Idec the license under Section 4.1.1(b) with respect to such Biogen Idec Alternate Modality Target, and (D) Section 2.1.1(c) will not apply with respect to such Biogen Idec Alternate Modality Product. For the avoidance of doubt, nothing in this Agreement shall restrict Biogen Idec's or its Affiliate's or licensee's discovery, research, development, manufacture, or commercialization of a product for a Pre-Existing Target that is not an oligonucleotide designed to bind to the RNA that encodes such Pre-Existing Target.

2.1.2. **Limitations and Exceptions to Isis' Exclusivity Covenants**. Notwithstanding anything to the contrary in this Agreement, Isis' practice of the following will not violate Section 2.1.1, Section 2.2 or Section (d) of APPENDIX 3:

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

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

(c) The research, development or commercialization of a Multi-Indication Compound to the extent permitted under APPENDIX 3; and

(d) The exercise of its rights under Section 3.2.2.

2.1.3. **Effect of Exclusivity on Indications**. The Compounds are designed to bind to the RNA that encodes a Collaboration Target with the intent of treating a Neurological Disease in the Field. Isis and Biogen Idec are subject to exclusivity obligations under Section 2.1; *however*, the Parties acknowledge and agree that, except as otherwise provided herein, each Party and its Affiliates (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* (i) a High Interest Target to the extent Section 2.1.1(a) still applies, (ii) a Biogen Idec Alternate Modality Target to the extent Section 2.1.1(c) still applies, or (iii) a Collaboration Target, in each case for any indication, even if such products are designed to treat a Neurological Disease.

2.2. **Right of First Negotiation for Follow-On Compounds**. On a Collaboration Program-by-Collaboration Program basis, during the period commencing on the Effective Date and ending upon (i) if the applicable Option is not exercised in accordance with this Agreement, [***], or (ii) if the applicable 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:

2.2.1. 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***").

2.2.2. 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 2.2.1 and this Section 2.2.2 will reset and Isis will provide Biogen Idec with a new Follow-On Negotiation Notice.

2.2.3. Any Follow-On Agreement entered into by Isis with a Third Party in accordance with Section 2.2.2 will be a Permitted License to the extent related to the Follow-On Compound.

2.2.4. 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 2.2, *unless* Isis enters into a Follow-On Agreement with a Third Party pursuant to this Section 2.2 and the terms of such agreement do not permit Isis to grant Biogen Idec rights with respect to the applicable Follow-On Compound.

Except as expressly set forth in Section 2.1.2, Section 2.2, or Section 10.4.4, in no event will Isis have the right to [***].

ARTICLE 3.
EXCLUSIVE OPTION

3.1. Option.

3.1.1. **Advance Data Disclosure**. On or about 90 days before the date on which Isis estimates that the database will be locked for the first PoC Trial for a particular Collaboration Program that is being conducted by Isis (each an "***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 for the applicable Collaboration Program 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 [***] for the applicable Collaboration Program 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 for the applicable Collaboration Program, *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**. On a Collaboration Program-by-Collaboration Program basis where Isis conducts the first PoC Trial, Isis will provide to Biogen Idec or its designated Affiliate (i) a copy of the most recent Investigator's Brochure for the applicable Collaboration Product, (ii) written notice from Isis regarding completion of the first PoC Trial, and (iii) the PoC Data Package for such Collaboration Program, 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 [***] days after database lock for the PoC Trial for such Collaboration Program. 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**. On a Collaboration Program-by-Collaboration Program basis, Isis hereby grants to Biogen Idec and its Affiliates an exclusive

option to obtain the license set forth in Section 4.1.1(a) with respect to such Collaboration Program (each an "***Option***"). Each Option for a Collaboration Program that is not an ALS Collaboration Program 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 for the applicable Collaboration Program (the "***Standard Option Deadline***"). Each Option for an ALS Collaboration Program will be available to Biogen Idec and its Affiliates until 5:00 pm (Eastern Time) on the earlier of (A) the [***] following Biogen Idec's receipt of the data generated under the statistical analysis plan after initial database lock for the first PoC Trial for the applicable ALS Collaboration Program, and (B) the [***] of the date a Development Candidate under such ALS Collaboration Program was designated (the ***"ALS Option Deadline***"); *provided however,* if Biogen Idec determines that an HSR Filing is required to be made under the HSR Act to exercise an 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 applicable Option, and (ii) pays to Isis the license fee set forth in Section 6.6, Isis will, and hereby does, grant to Biogen Idec or its designated Affiliate the license set forth in Section 4.1.1(a). 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 6.6, then Biogen Idec's Option for the applicable Collaboration Program will expire.

3.1.4. **HSR Compliance**.

(a) **HSR Filing**. If Biogen Idec notifies Isis pursuant to Section 1.7 or Section 3.1.3 that an HSR Filing is required for Biogen Idec to receive the license under Section 4.1.1(b) or exercise an 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. **Changing or Adding Modalities.**

3.2.1. **Changing to a Collaboration Target**. Provided that Biogen Idec has complied with its diligence obligations under Section 2.1.1(c) and Section 5.1.2, at any time during the Research Term after Biogen Idec has made the applicable payment under Section 6.2.2 with respect to a Biogen Idec Alternate Modality Product, subject to Section 3.2.3(a), Biogen Idec may elect to change such Biogen Idec Alternate Modality Target to a Collaboration Target upon written notice to Isis. Thereafter, (i) Biogen Idec will pay Isis the milestone payment under Section 6.2.1 (as such payment may be modified pursuant to Section 3.2.3(a)), such payment to be made within [***] days after Biogen Idec's notice under this Section 3.2.1, (ii) Isis will prepare and submit to the Neurology JRC an ASO Development Candidate Identification Plan for such Collaboration Target within [***] days after receipt of Biogen Idec's notice pursuant to this Section 3.2.1, which plan will be agreed upon as provided in Section 1.10.1(a), (iii) the Parties will seek to discover and develop a Development Candidate for such target pursuant to such plan and the provisions of this Agreement and (iv) such target will no longer be a Biogen Idec Alternate Modality Target hereunder.

3.2.2. **Changing to a Biogen Idec Alternate Modality Target**. At any time during the Term after Biogen Idec has made the applicable payment under Section 6.2.1 for a Collaboration Program, Biogen Idec may elect to change the applicable Collaboration Target under such Collaboration Program to a Biogen Idec Alternate Modality Target upon written notice to Isis, in which case the provisions of Section 3.2.3(b) will apply, and as of the date of such notice, Isis will be deemed to have granted Biogen Idec the license under Section 4.1.1(b) with respect to such target and such target will no longer be a Collaboration Target hereunder; *provided*, *however*, that Biogen Idec will not have the right to change a Collaboration Target to a Biogen Idec Alternate Modality Target if such Collaboration Target is a Pre-Existing Target. Within [***] days of the later of (i) Isis' receipt of Biogen Idec's notice electing to change a particular Collaboration Target to a Biogen Idec Alternate Modality Target, and (ii) Isis' receipt of the

data generated under the statistical analysis plan after initial database lock for any ongoing Clinical Study under the applicable Collaboration Program, by written notice to Biogen Idec, Isis may elect to either (1) cease all development activities under this Agreement relating to any ASO designed to bind to the applicable Biogen Idec Alternate Modality Target (i.e., the former Collaboration Target), until otherwise permitted to conduct such development activities under Section 2.1.1(c), or (2) subject to Section 3.2.3(b), continue to develop and commercialize on its own or with a Third Party such ASOs (or any other oligonucleotides) designed to bind to the applicable Biogen Idec Alternate Modality Target (i.e., the former Collaboration Target). If Isis makes an election under clause (2) of this Section 3.2.2, then Section 10.4.3(d) will apply to such former Collaboration Target.

3.2.3. Economics for Changing Modalities.

(a) If, pursuant to Section 3.2.1, Biogen Idec elects to change a Biogen Idec Alternate Modality Target to a Collaboration Target, the provisions related to Collaboration Programs under this Agreement, including to Sections 6.2, 6.4, 6.6, 6.7, and 6.10 will apply with respect to such Collaboration Target, *provided however* that (i) if Biogen Idec paid Isis the milestone payment under Section 6.2.2 with respect to such target prior to the date such target changed to a Collaboration Target, then the milestone payment under Section 6.2.1 with respect to such Collaboration Target will be reduced to $[***], (ii) if Biogen Idec paid Isis a milestone payment under Section 6.3 with respect to such target prior to the date such target changed to a Collaboration Target, then Biogen Idec may credit the amount of such payments against the amounts due Isis under Sections 6.6 and, to the extent applicable, Section 6.7.

(b) If, pursuant to Section 3.2.2, Biogen Idec elects to designate a Collaboration Target as a Biogen Idec Alternate Modality Target, the provisions related to Biogen Idec Alternate Modality Programs under this Agreement, including Sections 6.3 and 6.9 will apply with respect to such Biogen Idec Alternate Modality Target; *provided however* that (i) if the Collaboration Target Biogen Idec changed to a Biogen Idec Alternate Modality Target was not an ALS Target, then no payment will be due under Section 6.2.2 with respect to such Biogen Idec Alternate Modality Target and (ii) if Isis elects to continue to develop and commercialize such oligonucleotides under clause (2) of Section 3.2.2 Biogen Idec will not be required to pay Isis any un-accrued milestone payments or royalties under Section 6.3 and Section 6.9 *solely* with respect to the applicable Biogen Idec Alternative Modality Product Developed and Commercialized by Biogen Idec as a result of its conversion to a Biogen Idec Alternative Modality Target under Section 3.2.2.

3.2.4. Adding an Additional Modality.

3.2.4.1 **Adding a Collaboration Target**. Provided that Biogen Idec has complied with its diligence obligations under Section 2.1.1(c) and Section 5.1.2, at any time during the Research Term after Biogen Idec has made the applicable payment under Section 6.2.2 with respect to a Biogen Idec Alternate Modality Target, Biogen Idec may elect to add such Biogen Idec Alternate Modality Target as a Collaboration Target upon written notice to Isis. Thereafter, (i) Biogen Idec will pay Isis the milestone payment under Section 6.2.1, such payment to be made within [***] days after Biogen Idec's notice under this Section 3.2.4.1, (ii) Isis will prepare and submit to the Neurology JRC an ASO Development Candidate Identification Plan for such Collaboration Target within [***] days after receipt of Biogen Idec's notice pursuant to this Section 3.2.4.1, which plan will be agreed upon as provided in Section 1.10.1(a) and the Parties will seek to discover and develop a Development Candidate for such target pursuant to such plan and the provisions of this Agreement (including, for the avoidance of doubt, the provisions of ARTICLE 6), (iii) Section 2.1.1(c) will not apply with respect to any activities conducted by Isis pursuant to a Neurology Plan with respect to such target and (iv) Biogen Idec may continue Developing, Manufacturing and Commercializing a Biogen Idec Alternate Modality Product for the applicable Biogen Idec Alternate Modality Target in accordance with the terms of this Agreement (including, for the avoidance of doubt, the provisions of ARTICLE 6).

3.2.4.2 **Adding a Biogen Idec Alternate Modality Target**. At any time during the Term after Biogen Idec has made the applicable payment under Section 6.2.1 for a Collaboration Program, Biogen Idec may elect to add such Collaboration Target as a Biogen Idec Alternate Modality Target upon written notice to Isis; *provided*, *however*, that Biogen Idec shall not have the right to add such Collaboration Target as a Biogen Idec Alternative Modality Target if such Collaboration Target is a Pre-Existing Target. Thereafter, (a) upon Biogen Idec's payment of the applicable milestone under Section 6.2.2, subject to Section 3.2.5, such payment to be made within [***] days after Biogen Idec's notice under this Section 3.2.4.2, (i) Isis will be deemed to have granted Biogen Idec the license under Section 4.1.1(b) with respect to such target and (ii) Biogen Idec may Develop, Manufacture and Commercialize a Biogen Idec Alternate Modality Product for the applicable Biogen Idec Alternate Modality Target in accordance with the terms of this Agreement (including, for the avoidance of doubt, the provisions of ARTICLE 6) and (b) the Parties will continue all activities under this Agreement with respect to the applicable Collaboration Program.

3.2.5. HSR Compliance with Respect to Biogen Idec Alternate Modality Targets. If Biogen Idec determines that an HSR Filing is required to be made under the HSR Act for Biogen Idec to receive the license under Section 4.1.1(b) with respect to any Biogen Idec Alternate Modality Target that is designated under Section 3.2.2 or Section 3.2.4.2 and notifies Isis of such determination within 10 days after the Biogen Idec's notice to Isis under such section, the Parties will promptly file an HSR Filing in accordance with Section 3.1.4 and the deadline for Biogen Idec to pay Isis the milestone payment (or, if applicable, a portion thereof as provided in Section 3.2.3) under Section 6.2.2 will be extended until 5:00 pm (Eastern Time) on the fifth Business Day after the HSR Clearance Date.

3.2.6. Changes One-Time Only. Once Biogen Idec has elected to change a Collaboration Target to a Biogen Idec Alternate Modality Target, or to change a Biogen Idec Alternate Modality Target to a Collaboration Target under Section 3.2.1 or Section 3.2.2, as applicable, Biogen Idec cannot exercise its rights under Section 3.2 to change such target back to a Collaboration Target or Biogen Idec Alternate Modality Target, as applicable, or add such a Collaboration Target or Biogen Idec Alternate Modality Target, as applicable, without Isis' written consent.

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

3.3.1. On a Collaboration Product-by-Collaboration Product and Biogen Idec Alternate Modality Product-by-Biogen Idec Alternate Modality Product basis, Isis hereby grants to Biogen Idec and its Affiliates an option (the "***Diagnostic Option***") to negotiate during the Full Royalty Period or Biogen Idec Alternate Modality Royalty Period, as applicable, the terms of an agreement under which [***]. The Diagnostic Option will be available to Biogen Idec and its Affiliates until the expiration of the [***] or [***], as applicable, for the applicable Collaboration Product or Biogen Idec Alternate Modality Product.

3.3.2. During the [***] or [***], as applicable, Isis (i) has the right to [***], and (ii) will not [***].

3.3.3. If, during the [***] or [***], as applicable, 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 Licenses.

(a) **Collaboration Products**. Subject to the terms and conditions of this Agreement, on a Collaboration Program-by-Collaboration Program basis, effective upon Biogen Idec's exercise of the Option for a particular Collaboration Program 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 Collaboration Products under such Collaboration Program in the Field.

(b) **Biogen Idec Alternate Modality Products**. Subject to the terms and conditions of this Agreement, on a Biogen Idec Alternate Modality Target-by-Biogen Idec Alternate Modality Target basis, effective upon the date Biogen Idec pays Isis the milestone payment under Section 6.2.2 for a particular Biogen Idec Alternate Modality Target, 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 Biogen Idec Alternate Modality Products in the Field.

4.1.2. Sublicense Rights; CMO Licenses.

(a) Subject to the terms and conditions of this Agreement, Biogen Idec will have the right to grant sublicenses under the licenses granted under Section 4.1.1(a) and Section 4.1.1(b) 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 [***] 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 [***] days after the execution thereof.

(b) In connection with Biogen Idec's selecting and engaging one or more CMOs to supply Clinical Supplies after a license is granted under Section 4.1.1, or supply API and Finished Drug Product for Commercialization, Isis will, at Biogen Idec's option, either (1) grant a license from Isis to [***] under the [***] to the extent necessary for [***], which Isis agrees it will grant to [***], or (2) permit Biogen Idec to grant a sublicense from Biogen Idec to [***]. For Collaboration Products, each such manufacturing agreement between Biogen Idec and a CMO will contain [***]. Biogen Idec will provide Isis with a true and complete copy of any manufacturing agreement entered into with a CMO within [***] days after the execution thereof. Notwithstanding the foregoing, if Isis fails to comply with the terms of this Section 4.1.2(b) 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 [***].

(c) **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 or to perform Biogen Idec Activities or Isis Activities, as applicable, 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 6.13, 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 the date the applicable license under Section 4.1.1 is granted hereunder. With respect to Collaboration Products, Isis will disclose to Biogen Idec any Third Party Obligations Isis believes apply to applicable Collaboration Products each time Isis provides (x) the [***]; (y) the [***]; and (z) the [***], 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 the date the applicable license under Section 4.1.1 is granted hereunder, Biogen Idec provides Isis with such a written notice to exclude certain Third Party Patent Rights and Know-How from such license, such Third Party Patent Rights and Know-How will not be included in the Licensed Technology licensed with respect to the applicable Products 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 the date the applicable license under Section 4.1.1 is granted hereunder, 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 with respect to the applicable Products under this Agreement.

4.1.5. **Trademarks for Products**. If Biogen Idec is granted a license under Section 4.1.1 for a particular Product, to the extent that (i) Isis owns any trademark(s) specific to such Product which Isis used prior to the date such license was granted, and (ii) Biogen Idec reasonably believes such trademark(s) would be necessary or useful for the marketing and sale of the applicable 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 the 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 date the applicable license under Section 4.1.1 is granted hereunder, 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. **Assignment to Biogen Idec**. After Biogen Idec has obtained the license for a particular Collaboration Program or Biogen Idec Alternate Modality Target 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 related to such Collaboration Program or Biogen Idec Alternate Modality Target in the Field 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 related to such Collaboration Program or such Biogen Idec Alternate Modality Target, and thereafter 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 [***] days of Biogen Idec obtaining the applicable license under Section 4.1.1.

4.2.2. **Grant Back to Isis**. 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 [***], (ii) to conduct activities under other ASO Development Candidate Identification Plans and Initial Development Plans, (iii) to [***] to the extent permitted by this Agreement, (iv) to [***] to the extent permitted under APPENDIX 3, and (v) to exercise Isis' rights under Section 2.1.1(f) (if applicable) or Section 3.2.2.

4.3. **Data Licenses**.

4.3.1. **Data License to Biogen Idec**. Isis hereby grants Biogen Idec a worldwide, non-exclusive, royalty-free, sublicenseable license under any data included in the Isis Program Know-How for (a) any use other than in connection with the development, manufacture or commercialization of an oligonucleotide and (b) use in connection with the development, manufacture or commercialization any oligonucleotide that is being developed or commercialized by the Parties under this Agreement or any Isis/Biogen Idec Preexisting Development Agreement.

4.3.2. **Data License to Isis**. Biogen Idec hereby grants Isis a worldwide, non-exclusive, royalty-free, sublicenseable license under any data included in the Biogen Idec Program Know-How solely for use in connection with the development, manufacture or commercialization of oligonucleotides to the extent permitted by this Agreement and any Isis/Biogen Idec Preexisting Development Agreement.

4.4. **Enabling Patent Licenses**.

4.4.1. **Future Licenses**. Subject to the terms and conditions of this Agreement (including Biogen Idec's exclusivity covenants under Section 2.1.1), prior to Option exercise, if necessary for Biogen Idec to conduct any Biogen Idec Activities that are Development activities with respect to any High Interest Target or Collaboration Target in accordance with this Agreement, upon Isis' receipt of a written request from Biogen Idec together with Biogen Idec's written agreement

[***] Isis [***] arising under any Third Party agreement as a result of granting Biogen Idec the license under this Section 4.4.1, Isis will grant to Biogen Idec a non-exclusive, royalty-free license under any Licensed Technology [***] to conduct such activities.

4.4.2. **Enabling Patent License to Biogen Idec**. Subject to the terms and conditions of this Agreement (including Biogen Idec's exclusivity covenants under Section 2.1.1), Isis hereby grants Biogen Idec an irrevocable, worldwide, non-exclusive, sublicenseable license under any Isis Program Technology to research, develop, manufacture, have manufactured and commercialize (a) a product that is being developed or commercialized by the Parties under any Isis/Biogen Idec Preexisting Development Agreement, and (b) products that do not include an oligonucleotide as an active pharmaceutical ingredient. Such license in clause (b) above is royalty-free; *except* that if a product being sold by Biogen Idec, its Affiliates or sublicensee is Covered by a Target Related Isis Program Claim, then on a country-by-country basis Biogen Idec will pay Isis a royalty equal to [***]% of Net Sales of any product sold by Biogen Idec, its Affiliates or sublicensees so long as such product is Covered by such Target Related Isis Program Claim in such country. A ***"Target Related Isis Program Claim"*** means a Valid Claim that (i) is within an Isis Program Patent that is solely owned by Isis, (ii) Covers a product being sold by Biogen Idec, its Affiliates or Sublicensee, and (iii) claims a gene target, or a method of modulating such gene target to achieve a prophylactic or therapeutic effect/benefit.

4.4.3. **Enabling Patent License to Isis**. Subject to the terms and conditions of this Agreement (including Isis' exclusivity covenants under Section 2.1.1), Biogen Idec hereby grants Isis an irrevocable, worldwide, non-exclusive, sublicenseable license under any Biogen Idec Program Technology to research, develop, manufacture, have manufactured and commercialize products that include an oligonucleotide as an active pharmaceutical ingredient (other than a product that is being developed or commercialized by the Parties under any Isis/Biogen Idec Preexisting Development Agreement). Such license is royalty-free; *except* that if a product being sold by Isis, its Affiliates or Sublicensee is Covered by a Target Related Biogen Idec Program Claim, then on a country-by-country basis Isis will pay Biogen Idec a royalty equal to [***]% of net sales of any product sold by Isis, its Affiliates or sublicensees, then so long as such product is Covered by such Target Related Biogen Idec Program Claim in such country. A ***"Target Related Biogen Idec Program Claim"*** means a Valid Claim that (i) is within a Biogen Idec Program Patent that is solely owned by Biogen Idec, (ii) Covers a product being sold by Isis, its Affiliates or Sublicensee, and (iii) claims a gene target, or a method of modulating such gene target to achieve a prophylactic or therapeutic effect/benefit.

4.5. **Ownership of and Assistance with Regulatory Filings**. If requested by Biogen Idec, 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 applicable Collaboration 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. Each CTD will be consistent with the Specific Performance Milestone Events for the applicable Collaboration Program. The Parties regulatory teams will submit such plan to the CSC, if still active. The Parties will act in good faith and mutually agree upon each such plan, *provided, however*, that, after exercising an Option for the applicable Collaboration Program, 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 exercising an Option for a particular Collaboration Program, if Biogen Idec requests, Isis will assist Biogen Idec in preparing regulatory filings for the Collaboration 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, utilizing the payment mechanism set forth in Section 1.14.

4.6. **Subcontracting**. Subject to the terms of this Section 4.6, 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. Each Party will be responsible for any income or non-income taxes that arise as a result of such Party's use of any Third Party subcontractors hereunder, including payroll, income, withholding, sales and use, VAT, customs, duties excise or property taxes, and such taxes will not be reimbursable expenditures.

4.7. **Technology Transfer after Option Exercise**. On a Collaboration Program-by-Collaboration Program basis, Isis will promptly, but no later than [***] after Biogen Idec exercises its Option for such Collaboration Program hereunder, deliver to Biogen Idec or one or more designated Affiliates:

4.7.1. **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 10.4.2, including transferring the IND for the applicable Development Candidate to Biogen Idec together with all regulatory documentation (including drafts) related to the applicable 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 for each Collaboration Program to transfer such

Isis Know-How under this Section 4.7.1. 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, using the payment mechanism set forth in Section 1.14.

4.7.2. **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 applicable 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(a). Upon Biogen Idec's request, subject to Section 4.1.2, Isis will provide up to [***] for [***] ([***]) of its time for each Collaboration Program to transfer such Manufacturing and Analytical Know-How under this Section 4.7.2 to any Third Party Manufacturing API, Clinical Supplies or Finished Drug Product on Biogen Idec's behalf solely to Manufacture API, Clinical Supplies or Finished Drug 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, using the payment mechanism set forth in Section 1.14.

4.7.3. **API and Product**. Upon Biogen Idec's written request, Isis will sell to Biogen Idec any bulk API, Clinical Supplies 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**.

5.1.1. **Collaboration Products**.

(a) Prior to Option exercise, Biogen Idec will use Commercially Reasonable Efforts to conduct (i) any Biogen Idec Activities on the timeline set forth in the applicable Neurology Plan, and (ii) except as provided under Section 1.10.2(c)(ii), for each ALS Collaboration Program all activities under each Initial Development Plan on the timeline set forth in the applicable Initial Development Plan. Without limiting the foregoing, Biogen Idec may discontinue Development under such an Initial Development Plan if after having consulted, and having given good faith consideration to the recommendations of the Neurology JDC and a mutually-agreed Third Party expert, Biogen Idec in good faith believes

that continuing such Development would (1) pose an unacceptable risk or threat of harm in humans, or (2) violate any Applicable Law, ethical principles, or principles of scientific integrity, in which case Biogen Idec will provide Isis with reasonable advance notice of such discontinuation, including the grounds for Biogen Idec's determination, and Section 10.4.3 will apply.

(b) Following an 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 applicable Products; and Biogen Idec will use Commercially Reasonable Efforts to Develop, Manufacture and Commercialize at least one Product from each Collaboration Program for which an Option has been exercised.

5.1.2. **Biogen Idec Alternate Modality Products**. Following the date a license is granted to Biogen Idec under Section 4.1.1(b) for a particular Biogen Idec Alternate Modality Product, 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 applicable Biogen Idec Alternate Modality Products; and Biogen Idec will use Commercially Reasonable Efforts to develop, manufacture and commercialize at least one Biogen Idec Alternate Modality Product for each Biogen Idec Alternate Modality Target.

5.1.3. **Multi-Indication Targets for Non-Neurological Indications**. Without limiting any of the foregoing, with respect to any plan for the development and commercialization of a Multi-Indication Target Biogen Idec has agreed to conduct pursuant to a plan mutually-agreed under APPENDIX 3, Biogen Idec will use Commercially Reasonable Efforts to develop, manufacture and commercialize at least one Product for such Multi-Indication Target in accordance with such agreed plan.

5.1.4. **Specific Performance Milestone Events for Collaboration Products**. Without limiting any of the foregoing, (i) following an Option exercise for Collaboration Programs that are not ALS Collaboration Programs, and (ii) following the designation of the Development Candidate for ALS Collaborations, Biogen Idec will use Commercially Reasonable Efforts to achieve the specific performance milestone events set forth in SCHEDULE 5.1.4, as such schedule may be updated from time to time in accordance with Section 1.10.2(d) ("***Specific Performance Milestone Events***") for a Collaboration Product on the timeline set forth in SCHEDULE 5.1.4; *provided*, *however*, [***].

5.1.5. **Development Results under ALS Collaboration Programs**. Without limiting the other provisions of this Agreement, promptly following its generation or receipt of the results of a [***] or a Clinical Study under an ALS Collaboration Program, as applicable, Biogen Idec will provide Isis (i) all study reports from

[***] studies for the applicable Collaboration Product that are intended to support an investigational new drug application, (ii) all study reports for any pre-clinical and clinical trials conducted by Biogen Idec for such Collaboration Product, (iii) the data generated under the [***] for the applicable PoC Trial(s), and (iv) copies of all filings submitted to Regulatory Authorities regarding such Collaboration Product.

5.1.6. **Integrated Development Plan for Products**. On a Product-by- Product basis, 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, including Product sales forecasts (each, an "***Integrated Development Plan***" or "***IDP***"). Biogen Idec will prepare the IDP no later than (i) [***] after Option exercise for a Collaboration Product or (ii) after the First Commercial Sale of a Biogen Idec Alternative Modality Product, 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 the CSC [***] (or Isis after the CSC terminates under Section 1.17.5). 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 the CSC (or Isis after the CSC terminates under Section 1.17.5) for incorporation in the final IDP. Notwithstanding the foregoing, Biogen Idec's obligations to provide Isis with information or reports with respect to a Product under this Section 5.1.6 will terminate if [***].

5.1.7. **Investigator's Brochure for Collaboration Products**. After Option exercise, Isis will provide to Biogen Idec an up-to-date version of the Investigator's Brochure for the applicable Collaboration Product. Biogen Idec will keep Isis reasonably informed with respect to the status, activities and progress of Development of Collaboration Products by providing updated versions of the Investigator's Brochure for each Collaboration Product to Isis [***] and when Development of such Collaboration Product results in any substantive change to the safety or risk to the Collaboration Product. Biogen Idec's obligations under this Section 5.1.7 will terminate with respect to a Collaboration Product if [***].

5.1.8. **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. **Regulatory Matters; Global Safety Database; Pharmacovigilance Agreement**.

5.2.1. **IND-Holder Prior to Option Exercise**. Subject to this Section 5.2, for Collaboration Programs that are not ALS Collaboration Programs, Isis will be the IND-holder and will be responsible for all communications with Regulatory

Authorities regarding such Collaboration Programs prior to the applicable Option exercise. Subject to this Section 5.2, for ALS Collaboration Programs, Biogen Idec will be the IND-holder and will be responsible for all communications with Regulatory Authorities regarding such ALS Collaboration Programs.

5.2.2. **Pharmacovigilance Agreement**. As soon as reasonably practicable following designation of a particular Development Candidate, and in any event no later than [***] prior to the date on which Isis anticipates filing an IND for the associated Collaboration 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 such Collaboration 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 Isis/Biogen Idec Preexisting Development Agreements. In addition, following the Effective Date the Parties will discuss in good faith the possibility of entering into a single Safety Drug Exchange Agreement with respect to all activities under this Agreement and the Isis/Biogen Idec Preexisting Development Agreements. No later than [***] days prior the date on which Biogen Idec reasonably anticipates that it will exercise an Option, Biogen Idec will 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 the applicable Collaboration 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 Collaboration Product will be the global commercial safety database owner for such Collaboration 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 applicable Option, the Parties will communicate updates on safety data regarding a Collaboration Product to Biogen Idec through monthly telephone calls between the drug safety representatives of Biogen Idec and Isis. Biogen Idec and Isis will jointly review and discuss safety issues arising under any Collaboration Program that may have implications on any Initial Development Plan for such Collaboration Program. Biogen Idec may suggest actions to address Collaboration Product safety data or 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.

5.2.3. **Regulatory Communications Regarding Clinical Study Trial Designs**.

(a) The Party who is the IND-holder will not initiate discussions with a Regulatory Authority regarding the [***] for a Collaboration Program until such [***] have been established pursuant to Section 1.10.2(d), as applicable.

(b) To the extent practical, prior to any scheduled meeting with a Regulatory Authority regarding the [***] for a Collaboration Program, (i) the applicable Neurology JDC (or the Parties after such Neurology JDC terminates under Section 1.17.5) will discuss and mutually agree upon the timing and objectives for such meeting and (ii) the Party who is the IND-holder will provide the other Party with (A) an invitation to attend at least [***] and (B) an [***] with the IND-holder. In addition, the IND-holder will allow the other Party to participate in any such meeting under the direction of The IND-holder.

(c) In each case, to the extent regarding the [***] for a Collaboration Program, the Party who is the IND-holder will promptly provide the other Party with (i) final copies of all material correspondence with and submission to any Regulatory Authority promptly following submission thereof, (ii) a [***] from a Regulatory Authority, and (iii) a [***] with a Regulatory Authority.

(d) The Party who is the IND-holder will provide the other Party with [***] any Regulatory Authority that materially impact the [***] for a Collaboration Program sufficiently [***] to the applicable Regulatory Authority to enable the other Party to have a meaningful [***] thereof. The [***] any Regulatory Authority must reflect the Initial Development Plan. The applicable Neurology JDC (or the Parties after such Neurology JDC terminates under Section 1.17.5) will [***] on the [***]; *provided* that if [***] prior to a Regulatory Authority's requirement for a response as determined by [***] will consider in good faith [***].

5.2.4. **Isis' Participation in Regulatory Meetings for Collaboration Products**. 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 Collaboration Product or that directly relate to Isis' antisense oligonucleotide chemistry platform, and will allow Isis to participate in any such meetings under the direction of Biogen Idec.

5.2.5. **Regulatory Communications for Collaboration Products**. 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 Collaboration 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.

5.2.6. **Class Generic Claims for Collaboration Products**. To the extent Biogen Idec intends to make any claims in a Collaboration 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.

5.2.7. **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, 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 Collaboration Product as soon as practicable following the date such information is available to Biogen Idec (but not later than [***] 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 Collaboration Product, 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 [***] 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 5.2.7(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 Collaboration 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 5.2.7(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 Collaboration Product (including any potential class-related toxicity), Isis will promptly (and in no event later than five Business Days following identification by Isis) inform Biogen Idec of such issues and, if requested, provide the data supporting Isis' conclusions.

ARTICLE 6.
FINANCIAL PROVISIONS

6.1. **Up-Front Fee**. Within five Business Days following the Effective Date, Biogen Idec will pay Isis an up-front fee of $100,000,000.

6.2. **Drug Discovery Milestone Payments**.

6.2.1. **Collaboration Targets**. For each Collaboration Program, after (a) the Neurology JRC or Biogen Idec designates the applicable High Interest Target as a Collaboration Target under this Agreement and (b) Isis begins designing human development candidates under such Collaboration Program for human candidate screening under the applicable ASO Development Candidate Identification Plan ([***]), Isis will so notify Biogen Idec (such notice, the "***Design Notice***") and Biogen Idec will pay Isis a milestone payment equal to (i) $[***] for Collaboration Programs that are not ALS Collaboration Programs, subject to any applicable credits permitted by Section 1.8.3 or Section 1.8.4, or (ii) $[***] for ALS Collaboration Programs.

6.2.2. **Biogen Idec Alternate Modality Targets**. On a Biogen Idec Alternate Modality Target-by-Biogen Idec Alternate Modality Target basis, each time a Neurology Target is designated a Biogen Idec Alternate Modality Target under this Agreement, Biogen Idec will pay Isis a milestone payment equal to $[***], subject to any applicable credits permitted by Section 1.8.3 or Section 1.8.4.

6.3. **Milestone Payments for Achievement of Milestone Events by Biogen Idec Alternate Modality Products**. Subject to Section 3.2.3(b), for each Biogen Idec Alternate Modality Target, Biogen Idec will pay to Isis the milestone payments as set forth in TABLE X below when a milestone event (each, a "***Biogen Idec Alternate Modality Milestone Event***") listed in TABLE X is first achieved by a Biogen Idec Alternate Modality Product related to such Biogen Idec Alternate Modality Target:

TABLE X

Biogen Idec Alternate Modality Milestone Event	Milestone Event Payment per Biogen Idec Alternate Modality Target
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]

6.4. **Non-ALS Collaboration Program Milestone Payments for Achievement of Pre-Licensing Milestone Events**. As further consideration for Biogen Idec's Options, on a Collaboration Program-by-Collaboration Program basis where such a Collaboration Program is not an ALS Collaboration Program, Biogen Idec will pay to Isis the milestone payments as set forth in TABLE 1 below when a milestone event (each, a "***Standard Pre-Licensing Milestone Event***") listed in TABLE 1 is first achieved by a Collaboration Product under such Collaboration Program:

TABLE 1

Standard Pre-Licensing Milestone Event	Milestone Event Payment per Collaboration Program that is not an ALS Collaboration Program
[***]	$ [***]
[***]	[***]
[***]	[***]

On a Collaboration Program-by-Collaboration Program basis, where such a Collaboration Program is not an ALS Collaboration Program, 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 Collaboration Product under such Collaboration Program, even if Biogen Idec has exercised the applicable 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 reduced to $[***].

6.5. **ALS Collaboration Program Milestone Payments for Achievement of Pre-Licensing Milestone Events**. As further consideration for Biogen Idec's Options, on an ALS Collaboration Program-by-ALS Collaboration Program basis, Biogen Idec will pay to Isis

the milestone payments as set forth in TABLE 2 below when a milestone event (each, an "***ALS Pre-Licensing Milestone Event***") listed in TABLE 2 is first achieved by a Collaboration Product under such a Collaboration Program. Subject to the penultimate paragraph of Section 6.7, the amount of the payment for such Milestone Events will be determined based on whether or not such ALS Collaboration Program is a [***] Collaboration Program.

TABLE 2

ALS Pre-Licensing Milestone Event	Column 1 Milestone Event Payment per ALS Collaboration Program that is not a [***] Collaboration Program	Column 2 Milestone Event Payment per [***] Collaboration Program
[***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]

On an ALS Collaboration Program-by-ALS Collaboration Program basis, Biogen Idec will pay to Isis the Milestone Event payments as set forth in TABLE 2 after the applicable Milestone Event is first achieved by a Collaboration Product under such an ALS Collaboration Program, even if Biogen Idec has exercised the applicable Option prior to achievement of the Milestone Event.

6.6. **License Fee**. On an Option-by-Option basis, together with Biogen Idec's written notice to Isis stating that Biogen Idec is exercising such Option in accordance with this Agreement, Biogen Idec will pay to Isis a license fee of $[***]; *provided, however*, that if (i) Biogen Idec exercises the Option prior to the [***], the license fee for such Option will be [***] or (ii) Biogen Idec exercises the Option to a [***] Collaboration Program, subject to the last paragraph of Section 6.7, the license fee for such Option will be [***].

6.7. **Milestone Payments for Achievement of Post-Licensing Milestone Events**. On a Collaboration Program-by-Collaboration Program basis, Biogen Idec will pay to Isis the milestone payments as set forth in TABLE 3 below when a milestone event (each, a *"**Post-Licensing Milestone Event**"*) listed in TABLE 3 is first achieved by a Collaboration Product under such Collaboration Program, where (subject to the last paragraph of Section 6.7) the amount of the payment for such Milestone Event will be determined based on whether or not such Collaboration Program is a [***] Collaboration Program:

TABLE 3

Post-Licensing Milestone Event	Column 1 Milestone Event Payment per Collaboration Program that is not a [***] Collaboration Program	Column 2 Milestone Event Payment per [***] Collaboration Program
[***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]

On a Collaboration Program-by-Collaboration Program basis, if Biogen Idec exercises an Option for a Collaboration Program that is not a [***] Collaboration Program, 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 3 above.

If, with respect to a particular [***] Collaboration Program, Biogen Idec Initiates a Phase 2 Trial in an indication other than [***] (e.g., [***] or a [***] indication) Biogen Idec will pay Isis [***] within [***] days of the Initiation of such Phase 2 Trial.

If, with respect to a particular [***] Collaboration Program, Biogen Idec Initiates a Phase 3 Trial or files for Approval in an indication other than [***] (e.g., [***] or a [***] indication) such Collaboration Program will thereafter be a Collaboration Program (and not a [***] Collaboration Program) under this Agreement, and Biogen Idec will pay Isis (i) $[***] and (ii) [***] within [***] days of the Initiation of such Phase 3 Trial or filing for Approval.

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

6.8.1. On a Collaboration Product-by-Collaboration Product basis, the [***] milestone payment in TABLE 3 is creditable against the first Milestone Event payment for [***]. For example, if the [***] Milestone Event is achieved by a Collaboration Product in the United States, then the milestone payment for such Milestone Event is creditable against the first to occur of the (i) [***] (ii) [***] or (iii) [***] milestone payments for such Collaboration Product.

6.8.2. On a Biogen Idec Alternate Modality Target-by-Biogen Idec Alternate Modality Target basis, each milestone payment set forth in TABLE X above will be paid only once upon the first achievement of the Milestone Event regardless of how many Biogen Idec Alternate Modality Products related to such Biogen Idec Alternate Modality Target achieve such Milestone Event.

6.8.3. On a Collaboration Program-by-Collaboration Program basis, each milestone payment set forth in TABLE 1, TABLE 2 and TABLE 3 above will be paid only once

upon the first achievement of the Milestone Event regardless of how many Collaboration Products under such Collaboration Program achieve such Milestone Event.

6.8.4. 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. Similarly, if a Party proceeds directly to [***] without achieving the [***] then upon achieving the [***] Milestone Event, both the [***] and [***] Milestone Event payments are due. If Biogen Idec [***] for a Biogen Idec Alternate Modality Product, then both the [***] milestone payment and the [***] milestone payment will be due upon [***].

6.8.5. 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 five Business Days) following the date of achievement of such Milestone Event and such payment will be due within [***] days of the date such notice was delivered.

6.9. **Royalty Payments to Isis for Biogen Idec Alternate Modality Products**.

6.9.1. **Royalties for Biogen Idec Alternate Modality Products**. As partial consideration for the rights granted to Biogen Idec hereunder, subject to the provisions of Section 3.2.3(b) and Section 6.9.2, Biogen Idec will pay to Isis a [***]% royalty on Annual worldwide Net Sales of Biogen Idec Alternate Modality Products sold by Biogen Idec, its Affiliates or Sublicensees, on a country-by-country basis (the "***Biogen Idec Alternate Modality Royalty***").

6.9.2. **Royalty Period for Biogen Idec Alternate Modality Products**. Biogen Idec's obligation to pay Isis the Biogen Idec Alternate Modality Royalty above with respect to a Biogen Idec Alternate Modality Product will continue on a country-by-country and Biogen Idec Alternate Modality Product-by-Biogen Idec Alternate Modality Product basis from the date of First Commercial Sale of such Biogen Idec Alternate Modality Product until the [***] anniversary of the First Commercial Sale of such Biogen Idec Alternate Modality Product in such country (such royalty period, the "***Biogen Idec Alternate Modality Royalty Period***"); *provided, that* Biogen Idec will pay [***] (if applicable) for as long as Biogen Idec, its Affiliates or Sublicensees are selling Biogen Idec Alternate Modality Products.

(a) Biogen Idec will pay Isis royalties on Net Sales of Biogen Idec Alternate Modality 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 6.14.

(b) No royalties are due on Net Sales of Biogen Idec Alternate Modality Products arising from compassionate use and other programs providing for the delivery of Biogen Idec Alternate Modality Product at no cost.

(c) The sales of Biogen Idec Alternate Modality Products arising from named patient, compassionate use, or other similar programs will not be considered a First Commercial Sale for purposes of calculating the Biogen Idec Alternate Modality Royalty Period.

6.10. **Royalty Payments to Isis for Collaboration Products**.

6.10.1. **Biogen Idec Full Royalty for Collaboration Products**. As partial consideration for the rights granted to Biogen Idec hereunder, subject to the provisions of this Section 6.10.1 and Section 6.10.2, Biogen Idec will pay to Isis royalties on a Collaboration Program-by-Collaboration Program basis, on Annual worldwide Net Sales of Collaboration Products included in the applicable Collaboration Program sold by Biogen Idec, its Affiliates or Sublicensees, on a country-by-country basis, in each case in the amounts as follows in TABLE 4 below (the "***Biogen Idec Full Royalty***"):

TABLE 4

Royalty Tier	Annual Worldwide Net Sales of Collaboration Products for the Applicable Collaboration Program	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 of Collaboration Products will be calculated by [***].

(a) Biogen Idec will pay Isis royalties on Net Sales of Collaboration 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 6.14. No royalties are due on Net Sales of Collaboration Products arising from compassionate use and other programs providing for the delivery of Collaboration Product at no cost.

The sales of Collaboration 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.

6.10.2. **Application of Royalty Rates for Collaboration Products**. All royalties set forth under Section 6.10.1 are subject to the provisions of this Section 6.10.2, and are payable as follows:

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

(b) **Competition from Generic Products for Collaboration Products**. Subject to Section 6.11, on a country-by-country and Collaboration Product-by-Collaboration 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 such Collaboration Product in such country will be reduced to [***]% of the otherwise applicable Biogen Idec Full Royalty rate. For the purpose of determining the [***] for a particular Collaboration Product

under this Section 6.10.2(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 Collaboration Products are being sold.

(c) **Reduced Royalty Period for Collaboration Products**. Subject to Section 6.11, on a country-by-country and Collaboration Product-by-Collaboration 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 4 of Section 6.10.1, Biogen Idec will pay Isis royalty rates (the "***Biogen Idec Reduced Royalty***") on Net Sales of Collaboration 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) **End of Royalty Obligation for Collaboration Products**. On a country-by-country and Collaboration Product-by-Collaboration Product basis, other than [***], Biogen Idec's obligation to make royalty payments hereunder for such Collaboration Product 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 [***] for such Collaboration Product in such country and ending when the [***].

(e) **Royalty Examples**. SCHEDULE 6.10.2(e) attached hereto contains examples of how royalties will be calculated under this Section 6.10.

(f) **Allocation of Net Sales**. If, by reason of one or more royalty rate adjustments under this Section 6.10.2, different royalty rates apply to Net Sales of Collaboration Products from different countries, Biogen Idec will [***] such Net Sales [***]. SCHEDULE 6.10.2(f) attached hereto contains examples of how Net Sales of Collaboration Products from different countries at different royalty rates will be [***].

6.11. **Limitation on Aggregate Reduction for Royalties for Collaboration Products**.

6.11.1. In no event will the aggregate royalty reductions under Section 6.10.2(b) and Section 6.10.2(c) reduce the royalties payable to Isis on Net Sales of a Collaboration Product in any given period to an amount that is less than the [***] for such Collaboration Product.

6.11.2. In no event will the aggregate royalty offsets under Section 6.13.3(b) and Section 6.13.3(d) reduce the royalties payable to Isis on Net Sales of a Collaboration 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 6.13.3(b) and Section 6.13.3(d) will not apply during such Calendar Year but the full Royalty Quotient reduction pursuant to Section 6.10.2(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 4 of Section 6.10.1, then Biogen Idec may apply the offsets under Section 6.13.3(b) and Section 6.13.3(d) until the actual royalty payment made to Isis in such Calendar Year is equal to [***]% of the applicable royalty rates in TABLE 4 of Section 6.10.1.

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

6.12.1. **Reverse Royalty for a Discontinued Collaboration Product**. If Isis or any of its Affiliates or Sublicensees Commercializes a Discontinued Collaboration Product for which Biogen Idec has paid Isis the license fee under Section 6.5, then following the First Commercial Sale of such Discontinued Collaboration 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 Collaboration Product ("***Reverse Royalties***"). Isis' obligation to pay Biogen Idec Reverse Royalties will [***].

6.12.2. **Applicable Royalty Provisions**. In addition to this Section 6.12, 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 6.12, *mutatis mutandis*, including the provisions of Sections 6.10.2, 6.13, 6.14, 6.15, 6.16, and 6.17.

6.13. **Third Party Payment Obligations**.

6.13.1. **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(a) or Section 4.1.1(b) were in-licensed or were acquired by Isis under the agreements with Third Party licensors or sellers listed on SCHEDULE 6.13.1 or in a separate written agreement between the Parties (all 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 existing on the Effective Date as they apply to Collaboration Products for High Interest Targets designated as of the Effective Date, will be paid by [***] as [***].

6.13.2. **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(a) or Section 4.1.1(b) (as applicable) if Biogen Idec agrees in writing to pay Isis as [***].

6.13.3. **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(a), 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 6.11.2, 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 6.13.3(a) is Additional Core IP under Section 6.13.3(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 oligonucleotides, 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 6.13.3(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 6.13.3(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 [***].

6.13.4. **Other Third Party Payments**.

(a) **Isis' Third Party Agreements**. Except as otherwise expressly agreed to by Biogen Idec under Section 6.13.2, after Biogen Idec is granted the license under Section 4.1.1(a) or Section 4.1.1(b) for a particular Product, 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 6.13.3(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.

6.14. **Payments**.

6.14.1. **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, the exchange rate used and the type of Product (i.e., whether it is a Collaboration Product or Biogen Idec Alternate Modality Product). 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.

6.14.2. **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.

6.14.3. **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.

6.14.4. **No Payments for non-ASOs for Pre-Existing Targets**. For the avoidance of doubt, in no event shall any payments be due to Isis under this Agreement with respect to any non-oligonucleotide product developed or commercialized for a Pre-Existing Target.

6.15. **Audits**. After Biogen Idec is granted the license under Section 4.1.1(a) or Section 4.1.1(b) for a particular Product, 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 [***] days of receiving the Audit Report, with interest calculated in accordance with Section 6.17. 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.

6.16. **Taxes**.

6.16.1. **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.

6.16.2. **Withholding Tax**.

(a) 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, interest or penalties 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.

(b) With respect to any commercial supply agreement entered between the Parties for the commercial supply of API under this Agreement, such supply agreement will (i) provide that only Biogen Idec will claim any tax benefit allowed under IRC Section 199 Income Attributable to Domestic Production Activities, and (ii) include compensation to Isis reflecting the value of the reasonably anticipated tax benefit under IRC Section 199 Income Attributable to Domestic Production Activities forfeited by Isis. If the IRS determines that Biogen Idec is not entitled to the tax benefits under Section 199, Isis is not required to reimburse Biogen Idec for this tax benefit unless Isis receives a cash benefit on its federal tax return. A cash benefit will include any utilization of net operating losses that were generated in a year in which Isis claimed any IRC Sec 199 deduction. The reimbursement to Biogen Idec would be an amount equal to the Section 199 deduction times thirty-five percent, less any administrative costs to compute the tax benefit. The reimbursement would be due to Biogen Idec within 90 days after filing any original or amended Federal tax return. If the IRS determines that Isis is not eligible for the tax benefit or determines the tax benefit should be a different amount, Biogen Idec will pay back to Isis the amount of any adjustment. Isis will notify Biogen Idec within 30 days of filing a return that claims such deduction or utilizes a related net operating loss.

6.16.3. **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 determine if any taxes are applicable to payments under this Agreement and 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 6.16.

The provisions of this Section 6.16 are to be read in conjunction with the provisions of Section 12.4 below.

6.17. **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 (or the expiration or termination of) the last 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 each 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 a 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 or Biogen Idec (as applicable) will provide the Joint Patent Committee with notice of any Know-How or Patent Rights discovered, developed, invented or created jointly by such Party and a Third Party in the performance of activities under the Neurology Plans or solely by a Third Party performing activities under the Neurology Plans on such Party's behalf (such Know-How and Patents, the "***Collaborator IP***") promptly after such Party 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 applicable Development Candidate or any Compound under consideration by Isis for potential designation as a 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 applicable Development Candidate or any Compound under consideration by Isis for potential designation as the Development Candidate, at the non-contracting Party'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 the non-contracting Party.

(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 CSC'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 applicable 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. On a Collaboration Program-by-Collaboration Program basis or Biogen Idec Alternate Modality Target-by-Biogen Idec Alternate Modality Target basis (as applicable), until the earlier of the date Biogen Idec is granted the license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) and the expiration or termination of Biogen Idec's right to be granted such license, 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 the date Biogen Idec is granted the license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable), Isis will control and be responsible for all aspects of the Prosecution and Maintenance of all Licensed Patents that are the subject of such license grant, subject to Section 7.2.2(b) and Section 7.2.3. 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 License Grant. 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 such 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 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.

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 the date Biogen Idec is granted the license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable), Isis will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Program Patents Covering Products that are the subject of such license. After the date Biogen Idec is granted the license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable), Biogen Idec will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Program Patents Covering Products that are the subject of such license.

7.2.4. Prosecution of Multi-Indication Product-Specific Patents; Biogen Idec Supremacy to Enforce and Extend. With respect to Product Specific Patent Rights related to Multi-Indication Products, the Parties will endeavor to prosecute such Patent Rights to claim inventions related to Neurological Diseases separately from inventions related to Non-Neurological Indications. If there is an Isis Product-Specific Patent that Covers both (i) a Multi-Indication Product licensed to Biogen Idec under Section 4.1.1(a), and (ii) an Isis Multi-Indication Product (each

such Isis Product-Specific Patent, a "***Multi-Indication Product-Specific Patent***"), then so long as Biogen Idec is Developing and Commercializing such Multi-Indication Product pursuant to its license under Section 4.1.1(a), Biogen Idec will have the sole and exclusive right, but not the obligation, to institute and control any (i) Proceeding related to the infringement of such Multi-Indication Product-Specific Patent, (ii) Prosecution and Maintenance of such Multi-Indication Product-Specific Patent and (iii) patent term extension related to such Multi-Indication Product-Specific Patent.

7.2.5. 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 8.2.4(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 7.2.5, 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 Idec-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 7.2.5(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 Idec-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 7.2.5(b), Isis will have no obligation to notify Biogen Idec if Isis intends to abandon such Biogen Idec-Prosecuted Patent.

(c) Notwithstanding Section 7.2.5(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 6.10.2(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 7.2.5(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 Biogen Idec's right to obtain a license under Section 4.1.1 to such Isis Product-Specific Patent has not expired or terminated, Isis will notify Biogen Idec of such intention at least [***] 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 7.2.5(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 [***] 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 7.2.5(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 7.3.1, 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 the date the license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) is granted to Biogen Idec, 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 a Product, (a) Isis will have the first right, but not the obligation, to defend against any such Proceeding initiated prior to the date Biogen Idec is granted the license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) 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 the date Biogen Idec is granted the license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) 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 [***] 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 Collaboration 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 Collaboration 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 (e.g., a counterclaim of infringement), 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 (i) a product directed against the RNA that encodes a Collaboration Target in the Field, or (ii) a non-oligonucleotide product that is designed to bind, mimic or otherwise affect a protein or RNA that is encoded by a Biogen Idec Alternate Modality Target ("***Competitive Infringement***"), such Party will promptly notify the other Party in writing and will provide such other Party with available evidence of such Competitive Infringement; *provided, however*, that for cases of Competitive Infringement under Section 7.5.7 below, such written notice will be given within 10 days.

7.5.2. **Prior to License Grant**. For any Competitive Infringement with respect to a Product occurring after the Effective Date but before the date Biogen Idec is granted the license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable), 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 License Grant**. For any Competitive Infringement with respect to a particular Product (except for a Discontinued Collaboration Product) occurring after the date Biogen Idec is granted the license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable), 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 the date Biogen Idec is granted the license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) will be (i) [***]; or (ii) [***]; then

(c) any remaining proceeds constituting direct or actual damages for acts of infringement occurring after the date Biogen Idec is granted the license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) [***]; 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 6, neither Party may enter a settlement, consent judgment or other voluntary final disposition of a suit under this ARTICLE 6 that disclaims, limits the scope of, admits the invalidity or unenforceability of, or grants a license, 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 a 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 Collaboration 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 Collaboration Products, as applicable, regardless of which Party owns such Patent Rights.

7.8. **CREATE Act**. Notwithstanding anything to the contrary in this ARTICLE 6, neither Party will have the right to make an election under the CREATE Act when exercising its rights under this ARTICLE 6 without the prior written consent of the other Party, which will not be unreasonably withheld, conditioned or delayed. With respect to any such permitted election, the Parties will use reasonable efforts to cooperate and coordinate their activities with respect to any submissions, filings or other activities in support thereof. The Parties acknowledge and agree that this Agreement is a "*joint research agreement*" as defined in the CREATE Act.

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 6 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 6.13.2, (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 6, Isis retains the sole right to Prosecute and Maintain Isis Core Technology Patents and Isis Manufacturing and Analytical Patents during the Agreement Term and 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 the date Biogen Idec is granted the license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable), Biogen Idec will determine which relevant 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 each Collaboration Program.

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(a) upon the exercise of the Option for a Collaboration Product arising under the Collaboration Programs) 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 Collaboration 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 Collaboration Programs 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 with respect to Collaboration Products.

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 Collaboration Programs.

8.2.4. SCHEDULE 8.2.4(a) and SCHEDULE 8.2.4(b) set forth true, correct and complete lists of all Isis Core Technology Patents and Isis Manufacturing and Analytical Patents that apply to the Compounds contemplated under the Collaboration Programs as of the Effective Date (the "***Isis Platform Technology***"), 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.

8.2.5. 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 Platform Technology, Isis Manufacturing and Analytical Know-How, Isis Know-How, Collaboration Targets or High Interest Targets 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 Platform Technology, Isis Manufacturing and Analytical Know-How, Isis Know-How or High Interest Targets that would impact activities 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 Isis Core Technology Patent or Isis Manufacturing and Analytical 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 Isis Core Technology Patent or Isis Manufacturing and Analytical Patent is not properly identified on each patent, and (c) all official fees, maintenance fees and annuities for the Isis Core Technology Patent or Isis Manufacturing and Analytical Patent have been paid and all administrative procedures with governmental agencies have been completed.

8.2.7. Isis has set forth on SCHEDULE 6.13.1 or in a separate written agreement with Biogen Idec true, correct and complete lists of the agreements with Third Party licensors or sellers pursuant to which Isis has licensed or acquired the Licensed Technology Controlled by Isis as of the Effective Date licensed to Biogen Idec under Section 4.1.1(a) that is necessary or useful to conduct the research, Development, Manufacture or Commercialization of any High Interest Target listed on the High Interest Target List as of 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 with respect to the Isis Core Technology Patents and Isis Manufacturing and Analytical Patents that affect the rights granted by Isis to Biogen Idec under this Agreement with respect to Collaboration Programs.

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 8.2.4(a), SCHEDULE 8.2.4(b) and SCHEDULE 8.2.4(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 a 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 Collaboration 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 EACH PRODUCT IS THE SUBJECT OF ONGOING RESEARCH AND DEVELOPMENT AND THAT NEITHER PARTY CAN ASSURE THE SAFETY, USEFULNESS OR COMMERCIAL OR TECHNICAL VIABILITY OF EACH 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 a 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 it's 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 Collaboration 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 [***] 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 [***] 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 [***] days before Biogen Idec initiates the First Commercial Sale of a 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 10.4.4(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 all Products (or Discontinued Collaboration Product(s)) in such country;

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

10.1.3. where there are no Collaboration Targets and no Biogen Idec Alternate Modality Targets designated by the expiration of the Research Term as described in Section 1.9;

10.1.4. where there are no Biogen Idec Alternate Modality Targets designated by the expiration of the Research Term as described in Section 1.9, and no Development Candidates designated by the expiration of the ASO Development Candidate Identification Term as described in Section 1.10.1(c); and

10.1.5. where there are no Biogen Idec Alternate Modality Targets designated by the expiration of the Research Term as described in Section 1.9, and every Option has expired as a result of Biogen Idec not providing Isis a written notice stating Biogen Idec is exercising such Options and paying Isis the applicable license fees under Section 6.6 by the Option Deadline, or as a result of Section 1.10.2(g) or Section 10.4.3.

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 as a whole, or terminate this Agreement in part with respect to a particular Collaboration Program or Biogen Idec Alternate Modality Target, for convenience by providing 90 days written notice to Isis of such termination.

10.2.2. **Termination for Failure to Divest Directly Competitive Collaboration Product**. If a Competing Collaboration Acquirer or Competing Alternate Modality Acquirer, as applicable, does not, during the Collaboration Divestiture Period or Alternate Modality Divestiture Period, as applicable, divest itself of a Directly Competitive Collaboration Product, Directly Competitive Collaboration Program, Directly Competitive Alternate Modality Product or Directly Competitive Alternate Modality Program, as applicable, or terminate the development and commercialization of such Directly Competitive Collaboration Product or Directly Competitive Alternate Modality Product or activities under such Directly Competitive Collaboration Program or Directly Competitive Alternate Modality Program, as applicable, or assign this Agreement to a Third Party that is not itself developing or commercializing such a Directly Competitive Alternate Modality Product, or engaged in such Directly Competitive Collaboration Program or Directly Competitive Alternate Modality Program, as applicable, as set forth in Sections 12.5.2 and 12.5.3, Biogen Idec may terminate this Agreement solely with respect to the Collaboration Program or Biogen Idec Alternate Modality Program affected thereby 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 with respect to a proposed Biogen Idec Alternate Modality Program or Collaboration Program under Section 1.7, Section 3.1.3 or Section 3.2.5 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 solely with respect to the applicable proposed Biogen Idec Alternate Modality Program or Collaboration Program (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 related to such proposed Biogen Idec Alternate Modality Program or Collaboration Program, 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 with respect to a proposed Biogen Idec Alternate Modality Program or Collaboration Program, as applicable.

(b) If this Agreement is terminated with respect to a Collaboration Program 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 ARTICLE 1, 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 [***] days to cure such breach. If Isis fails to cure such breach within the [***] day period, or if the breach is not subject to cure, Biogen Idec may terminate this Agreement with respect to the Neurology Target or Collaboration Program affected by such breach 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 with respect to the Neurology Target or Collaboration Program affected by such breach.

(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 [***]-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 [***] 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 [***] days following such notice). If Biogen Idec fails to cure such breach within the [***] day or [***] day period, as applicable,

or if the breach is not subject to cure, Isis in its sole discretion may terminate this Agreement with respect to the Neurology Target or Collaboration Program affected by such breach by providing written notice thereof 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 ARTICLE 1 prior to the date Biogen Idec is granted a license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) with respect to a particular High Interest Target or Collaboration Program, Biogen Idec will notify Isis and, within [***] 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 ARTICLE 1. Following such a meeting, if Isis fails to use Commercially Reasonable Efforts as contemplated by ARTICLE 1 with respect to such High Interest Target or Collaboration Program, then subject to Section 10.2.6 below, Biogen Idec will have the right, at its sole discretion, to (i) terminate this Agreement as it relates to the applicable High Interest Target or Collaboration Program or, (ii) if the breach involves a Collaboration Program prior to Option exercise, Biogen Idec may elect to trigger the alternative remedy provisions of Section 10.3 below as it relates to the applicable Collaboration Program in lieu of terminating this Agreement for such Collaboration Program 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 ARTICLE 1 prior to the date Biogen Idec is granted a license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable).

(b) If Biogen Idec, in Isis' reasonable determination, fails to use Commercially Reasonable Efforts under Section 5.1 with respect to a Collaboration Program, Isis will notify Biogen Idec and, within [***] 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 with respect to the applicable Collaboration Program 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 as it relates to such Collaboration Program.

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 [***] 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 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 [***] 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.

10.3. **Alternative Remedies to Termination Available to Biogen Idec Prior to Option Exercise**. If, prior to Option exercise, with respect to a particular Collaboration Program Biogen Idec elects to (i) exercise the alternative remedy provisions of this Section 10.3 in lieu of terminating this Agreement for such Collaboration Program 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, *solely with respect to the Collaboration Program giving rise to Biogen Idec's exercise of these alternative remedy*

provisions, 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 Collaboration Product under the applicable Collaboration Program or participate in the Neurology JRC, the applicable Neurology JDC, JPC or any other subcommittees or working groups established pursuant to this Agreement. Biogen Idec will solely make all decisions that this Agreement would otherwise require or permit the Neurology JRC, the applicable Neurology JDC, 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 applicable Option;

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

(d) Biogen Idec may exclude Isis from all discussions with Regulatory Authorities regarding the applicable Collaboration 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 regarding the applicable Collaboration Products pursuant to this Agreement (including pursuant to Section 4.7 and Section 5.2.7) will terminate, other than reports required by Section 6.14.1, Section 10.4.4 (if applicable), and as reasonably required to permit Isis to perform its obligations under this Agreement; *provided* such remedy will not limit or diminish the scope of any licenses granted by Biogen Idec to Isis under this Agreement;

(f) Isis will perform its obligations under Section 4.7 with respect to the applicable Collaboration Product within [***] 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 applicable Collaboration Products in an efficient and orderly manner; and

(g) If such Collaboration Program is not an ALS Collaboration Program the financial provisions of ARTICLE 6 as they apply to such Collaboration Program will be modified as follows:

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

(ii) *License Fee*. The license fee set forth in Section 6.6 for the applicable Collaboration Product will be [***]. Such [***] will be due within 90 days after [***] and Biogen Idec's [***].

The milestone provisions of Section 6.7 and the royalty provisions of Section 6.10 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 Biogen Idec Alternate Modality Product or Collaboration Product (as applicable) that is the subject of 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, except to the extent such Confidential Information is necessary or useful to conduct activities for a surviving Product. 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) **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.

(c) **Survival**. The following provisions of this Agreement will survive the expiration or termination of this Agreement: Section 1.9 (End of Research Term), Section 1.10.1(c) (End of ASO Development Candidate Identification Term), Section 2.1.1(f) (Failure to Defer or Designate a High Interest Target a Collaboration Target or Biogen Idec Alternate Modality Target), Section 4.1.2(c) (Effect of Termination on Sublicenses), Section 4.2.2 (Grant Back to Isis), Section 4.3 (Data Licenses), Section 4.4.2 (Enabling Patent License to Biogen Idec), Section 4.4.3 (Enabling Patent License to Isis), Section 4.7 (Technology

Transfer after Option Exercise) (but only to the extent necessary to satisfy the requirements of Section 10.4.4), Section 6.12 (Reverse Royalty Payments to Biogen Idec for a Discontinued Collaboration Product), Section 6.14.3 (Records Retention), Section 6.15 (Audits), Section 7.1.1 (Isis Technology and Biogen Idec Technology), Section 7.1.2 (Agreement Technology), Section 8.4 (Disclaimer), ARTICLE 9 (Indemnification; Insurance), Section 10.2.3(b), Section 10.2.7 (Termination for Insolvency), Section 10.4 (Consequences of Expiration or Termination of the Agreement) (except Section 10.4.5 (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. **Natural Expiration**. If this Agreement expires in accordance with Section 10.1.1 or Section 10.1.2, the following terms will apply to any Biogen Idec Alternate Modality Product or Collaboration Product (as applicable) that is the subject of such expiration:

(a) **Perpetual, Royalty-Free Non-Exclusive License**. If Biogen Idec has been granted a license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) for a particular Product, then upon expiration of the Biogen Idec Alternate Modality Royalty Period or Reduced Royalty Period, as the case may be, in all countries in which the applicable Products are being or have been sold, Isis will and hereby does grant to Biogen Idec a perpetual, non-exclusive, worldwide, royalty-free, fully paid-up, sublicensable license under the Isis Know-How to Manufacture, Develop and Commercialize the applicable Product.

10.4.3. **Termination Before License Grant**. If this Agreement expires or is terminated by a Party in accordance with this ARTICLE 10 before Biogen Idec has been granted a license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) for a particular Product, then, in addition to the terms set forth in Section 10.4.1, the following terms will apply to each Product, Neurology Target, High Interest Target or Collaboration Program that is the subject of such expiration or termination:

(a) Biogen Idec's right to designate High Interest Targets as Collaboration Targets or Biogen Idec Alternate Modality Targets under this Agreement will expire and Isis will be free to Develop and Commercialize the applicable Product (and any other applicable Compounds) on its own or with a Third Party.

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

(c) Neither Party will have any further obligations under Section 2.1 of this Agreement with respect to the terminated Neurology Targets and Collaboration Program(s).

(d) To the extent requested by Isis, Biogen Idec will promptly (1) assign to Isis any manufacturing agreements with a CMO identified by Isis to which Biogen Idec is a party, solely to the extent such manufacturing agreements relate to the terminated Collaboration Program 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 terminated Collaboration Program(s) 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.

(e) If Biogen Idec terminates this Agreement for convenience with respect to a Collaboration Program after the 30th day following Biogen Idec's receipt of the Development Candidate Data Package for such Collaboration Program, but prior to Option exercise for such Collaboration Program, then Biogen Idec will [***].

(f) Except as explicitly set forth in Section 10.4.1(a), Section 10.4.1(b) or Section 10.4.1(c), Biogen Idec will have no further rights and Isis will have no further obligations with respect to each terminated Collaboration Program.

(g) If Biogen Idec terminates this Agreement for convenience with respect to an ALS Collaboration Program, then *solely with respect to such terminated ALS Collaboration Program*:

(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 applicable Discontinued Collaboration Product(s) solely as necessary to Develop, make, have made, use, sell, offer for sale, have sold, import and otherwise Commercialize the applicable Discontinued Collaboration Product(s) in the Field (such license will be sublicensable by Isis in accordance with Section 4.1.2, *mutatis mutandis*);

(ii) Biogen Idec will transfer to Isis for use with respect to the Development and Commercialization of the applicable Discontinued Collaboration Product(s), any Know-How, data, results, regulatory information, filings, and files in the possession

of Biogen Idec as of the date of such reversion to the extent related to such Discontinued Collaboration Product(s), and any other information or material specified in Section 4.7; and

(iii) To the extent requested by Isis, Biogen Idec will promptly assign to Isis any manufacturing agreements solely to the extent related to the applicable Discontinued Collaboration Products and identified by Isis to which Biogen Idec is a party.

10.4.4. **Termination After License Grant**. If this Agreement is terminated by a Party in accordance with this ARTICLE 10 after Biogen Idec has been granted a license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) for a particular Product, then, in addition to the terms set forth in Section 10.4.1, the following terms will apply to any Product or Collaboration Program that is the subject of such termination:

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

(b) Neither Party will have any further obligations under Section 2.1 of this Agreement with respect to the terminated Product, Neurology Target and Collaboration Program(s).

(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 Product, Neurology Target and Collaboration Program(s).

(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 *solely with respect to the terminated Products and/or Collaboration Program(s)*:

(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 applicable Discontinued Collaboration Product(s) solely as necessary to Develop, make, have made, use, sell, offer for sale, have sold, import and otherwise Commercialize the applicable Discontinued Collaboration Product(s) 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 and Isis' interest in any Program Patents that relate to the

applicable Biogen Idec Alternate Modality Product(s) and/or Discontinued Collaboration Product(s) 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 applicable Discontinued Collaboration Product(s), any Know-How, data, results, regulatory information, filings, and files in the possession of Biogen Idec as of the date of such reversion to the extent related to such Discontinued Collaboration Product(s), and any other information or material specified in Section 4.7;

(iv) Biogen Idec will license to Isis any trademarks that are specific to a Discontinued Collaboration Product(s) solely for use with such Discontinued Collaboration Product(s), 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 arising from the terminated Product and/or Collaboration Program, 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 [***] 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 6.12 with respect to the applicable Discontinued Collaboration Product(s). Such payments will be governed by the financial provisions in Section 6.14, and the definition of Net Sales will apply to sales of Discontinued Collaboration Product(s) by Isis, in each case *mutatis mutandis*.

(e) With respect to Discontinued Collaboration Products, 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 Idec will sell to Isis any bulk API, Clinical Supplies 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 solely to the extent related to the applicable Discontinued Collaboration Products and identified by Isis to which Biogen Idec is a party.

(g) If Biogen Idec under Section 10.2.1 or Section 10.2.2 voluntarily terminates its license under Section 4.1.1(b) with respect to a High Interest Target Biogen Idec designated as a Biogen Idec Alternate Modality Target then Section 2.1.1(f) will apply.

10.4.5. 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 *solely with respect to the Collaboration Programs that are the subject of the Isis Breach Event*:

(i) Terminate Isis' right to participate in the CSC, Neurology JRC, the applicable Neurology JDC, JPC and any other subcommittees or working groups established pursuant to this Agreement;

(ii) Terminate Isis' participation in any ongoing research and development programs under the applicable Collaboration Program 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 applicable Collaboration 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 applicable 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 related to the applicable Collaboration Products, including pursuant to Section 4.7 and Section 5.2.7, other than reports required by Section 6.14.1, Section 10.4.4 (if applicable), and as reasonably required to permit Isis to perform its obligations under this Agreement; *provided* such remedy will not limit or diminish the scope of any licenses granted by Biogen Idec to Isis under this Agreement; and

(vi) If Isis has not completed the Development activities that are its responsibility under the applicable ASO Development Candidate Identification Plan and Initial Development 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 applicable 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) *solely* with respect to the Collaboration Program that is the subject of the Isis Breach Event [***] (the "***Setoff Amount***"). If Biogen Idec exercises its setoff right under this Section 10.4.5(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 10.4.5(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 10.4.5(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 10.4.5(b) the Advisory Panel will determine (1) the amount (if any) that Biogen Idec may setoff against future payments *solely* with respect to the Collaboration Program that is the

subject of the Isis Breach Event 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 *solely* with respect to the Collaboration Programs that are the subject of the Isis Breach Event 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 6.17 (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 10.4.5(b); (Y) meet with the Advisory Panel as required in Section 3 of SCHEDULE 10.4.5(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 10.4.5(b) and SCHEDULE 10.4.5(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 a 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 License Grant**. Prior to the date Biogen Idec has been granted a license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) with respect to a Product, such 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 such 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 such 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 License Grant**. After the date Biogen Idec has been granted a license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) with respect to a Product, 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 such 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 such 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 for Collaboration Products**. Regarding any proposed scientific publications or public presentations related to summaries of results from any Clinical Studies generated by Isis or Biogen Idec for a Collaboration Product, the Parties acknowledge that scientific lead time is a key element of the value of the Collaboration Products 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 [***] 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 Collaboration Programs. If, during such [***] 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 [*** 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 [***] 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 a Product, the other Party's role in discovering and developing the Product or Discontinued Collaboration 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 [***] days after either Party notifies the other Party that the Dispute has not been resolved (*provided, that* such notice cannot be given less than [***] 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 [***] 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 CSC 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 CSC representatives also participate in such meeting, if desired. If the Executives fail to resolve the Dispute within such [***] 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 10.4.5(b) and SCHEDULE 10.4.5(b).

12.1.4. **Expert Resolution.** In the event that a matter is referred for expert resolution under this Section 12.1.4 pursuant to Section 1.10.2(d) or under APPENDIX 3, the matter will be resolved by a panel of three (3) industry experts experienced in the issues comprising such dispute. One expert will be chosen by Isis, one expert will be chosen by Biogen Idec and the third expert will be chosen by mutual agreement of the experts chosen by Isis and Biogen Idec. The place of such expert resolution will be in Chicago, Illinois. Within [***] days after the selection of the third expert (which will occur not later than [***] days after a Party notifies the other Party that it elects to have a dispute resolved pursuant to this Section

12.1.4), the Parties will each simultaneously submit to the expert panel and one another a written statement of their respective positions on the relevant dispute. Each Party will have [***] days from receipt of the other Party's submission to submit a written response thereto, which will include any scientific and technical information in support thereof. The expert panel will conduct at least one hearing at which each Party will have the opportunity to advocate its position before the other Party and the expert panel. The expert panel will have the right to further meet with both Parties together, as necessary to make a determination. There will be no *ex parte* communications between an individual Party and either the expert panel or one or more experts. All documents submitted will be in the English language. Further, the expert panel will have the right to request information and materials and to require and facilitate discovery as it will determine is appropriate in the circumstances, taking into account the needs of the Parties and the desirability of making discovery expeditious and cost-effective determinations. No later than 90 days after the designation of the third expert or as otherwise agreed by the Parties, the expert panel will make a determination. The expert panel will provide the Parties with a written statement setting forth the basis of the determination in connection therewith. The decision of the expert panel will be final, binding and conclusive, absent manifest error. Each Party will bear its attorneys' fees, costs and disbursements (including, for example, expert witness fees and expenses, photocopy charges, travel expenses, etc.) and the Parties will share equally (50/50) the fees and costs of the expert panel. Judgment upon any award rendered pursuant to this Section 12.1.4 may be entered by any court having jurisdiction over the Parties' assets. Except to the extent necessary to confirm or enforce an award or as may be required by law, neither Party nor any of the experts may disclose the existence, content or results of any proceeding under this Section 12.1.4 without the prior written consent of both Parties.

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 6.13.3(c)). Except for the offsets and credits explicitly set forth in Section 1.8.3, Section 6.15, Section 6.13.3(b), Section 6.13.3(d) and Section 10.4.5(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 [***] 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 a refund is due from Isis 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.

12.5.1. Research Activities. If, at any time during the Research Term, a Change of Control occurs, then at any time prior to the [***] anniversary of the closing of such Change of Control, upon written notice to Isis, Biogen Idec may either:

(a) Extend the Research Term until such time as Isis has completed target validating activities that are Isis Activities under the Neurological Disease Research Plan for a total of [***] High Interest Targets;

(b) Terminate the Research Term, in which case: (i) Isis will complete all ongoing target validation work that are Isis Activities under the Neurological Disease Research Plan and advance each such target to Target Sanction (but for clarity, no target validation work will be initiated for any new target under the Neurological Disease Research Plan); (ii) Isis will complete all ongoing Isis Activities under the Core Research Plan (but for clarity, no new work will be initiated under the Core Research Plan); (iii) for each Collaboration Target that is not an ALS Target that reaches Target Sanction or each ALS Target designated a Collaboration Target, an ASO Development Candidate Identification Plan will be prepared and Isis will carry out its obligations under such plan, all in accordance with Section 1.10.1; (iv) Isis will continue to perform its obligations under each ongoing ASO Development Candidate Identification Plan until the end of the applicable ASO Development Candidate Identification Term and under each ongoing Initial Development Plan until completion of all Isis Activities thereunder; (v) for each Collaboration Program for which a Development Candidate is identified as provided herein, Biogen Idec may, upon written notice to Isis, such notice to be delivered within [***] days after designating a Development Candidate for the applicable Collaboration Program, elect to either (A) exercise the applicable Option by notifying Isis in writing of Biogen Idec's election to license the Collaboration Product [***] and will be paid to Isis within [***] days after Biogen Idec's election under clause (A) of this Section 12.5.1(b),

and after such exercise, Biogen Idec will not be obligated [***], or (B) establish an Initial Development Plan for such Collaboration Program pursuant to Section 1.10.2(d), in which case Isis and Biogen Idec will continue to exercise their rights and perform their respective obligations with respect to the applicable Collaboration Program under the terms of this Agreement; (vi) the Research Term will end upon Isis' completion of all Isis Activities under clauses (i), (ii) and (iii) above; and (vii) within [***] days after the end of the Research Term, Isis will [***]; or

(c) Allow such [***] period to lapse without providing any such notice of election under this Section 12.5.1, in which case Isis and Biogen Idec will continue to exercise their rights and perform their respective obligations under the terms of this Agreement.

12.5.2. Collaboration Programs. On a Collaboration Program-by-Collaboration Program basis, if, at any time during the Option Period, a Change of Control occurs involving Isis and a Person that, at the time of the close of such Change of Control, is developing in human clinical trials or commercializing a Directly Competitive Collaboration Product within the Field or is engaged in a Directly Competitive Collaboration Program or, at any time during the Term after the closing of such Change of Control, develops or acquires a Directly Competitive Collaboration Product or begins a Directly Competitive Collaboration Program (such Person being hereinafter referred to as a "***Competing Collaboration Acquirer***") and such Competing Collaboration Acquirer has not, within [***] of either (i) the closing of the Change of Control in the event the Directly Competitive Collaboration Product is being developed in human clinical trials or commercialized, or the Directly Competitive Collaboration Program exists, as of such closing date or (ii) the date of first development or acquisition of such Directly Competitive Collaboration Product or the date on which such Competing Collaboration Acquirer begins such Directly Competitive Collaboration Program (the "***Collaboration Divestiture Period***") divested itself of the Directly Competitive Collaboration Product or Directly Competitive Collaboration Program, or terminated development and commercialization of such Directly Competitive Collaboration Product or such Directly Competitive Collaboration Program, then (A) Isis will provide written notice to Biogen Idec of the closing of such Change of Control or Collaboration Divestiture Period, as applicable, (B) [***], (C) solely with respect to any Collaboration Program that relates to such Directly Competitive Collaboration Product or Directly Competitive Collaboration Program for which Initiation of IND-Enabling Toxicology Studies have not occurred, subject to Section 12.5.3, elect to have Isis complete Isis Activities under this Agreement for such Collaboration Program until such time as the applicable Collaboration Program is ready to begin IND-Enabling Toxicology Studies, after which Biogen Idec may elect to exercise its rights under clause (D) of this Section 12.5.2 with respect to such Collaboration Program (in which case the applicable deadline for Biogen Idec's Notice under such clause will be extended until [***] after designation of a Development Candidate for

such Collaboration Program), and (D) solely with respect to any Collaboration Product affected by such Directly Competitive Collaboration Product or Directly Competitive Collaboration Program, Biogen Idec will have the right, within [***] following such written notice, to either:

(a) if unexercised, exercise the applicable Option by notifying Isis in writing of Biogen Idec's election to license the Collaboration Product at a prorated license fee payment as compared to the license fee payment set forth in Section 6.5, based upon the stage of Development of the applicable Collaboration Product at the time of Change of Control or Collaboration Divestiture Period, as applicable, which license fee payments are set forth on TABLE A of SCHEDULE 12.5 hereto. If Biogen Idec exercises the applicable Option pursuant to this Section 12.5.2(a), Biogen Idec will not be obligated [***]. Upon Biogen Idec's exercise of its Option pursuant to this Section 12.5.2(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 12.5.2, or otherwise provide Isis with written notice within such period electing not to exercise the applicable Option pursuant to Section 12.5.2(a) above, in either of which cases, subject to Section 12.5.3, Isis and Biogen Idec will continue to exercise their rights and perform their respective obligations with respect to the Collaboration Product under the terms of this Agreement.

Upon Biogen Idec's exercise of an Option pursuant to Section 12.5.2(a) above, Isis will carry out its technology transfer obligations pursuant to Section 4.7 with respect to the Collaboration Product. For the avoidance of doubt, except as set forth in this Section 12.5.2, 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.

12.5.3. Protective Provisions. At any time while Isis is conducting activities pursuant to Section 12.5.2(iii) or Section 12.5.2(b), to separate its Development activities under this Agreement from development activities relating to a Directly Competitive Collaboration Product ("***Directly Competing Development Activities***"), Isis will, and will cause the Competing Collaboration Acquirer to, (a) establish separate teams to conduct Development activities under this Agreement and such Directly Competing Development Activities and (b) prevent any Confidential Information relating to the Development of the applicable Collaboration Product from being disclosed to, or used by, individuals performing such Directly Competing Development Activities.

12.5.4. Biogen Idec Alternate Modality Programs. On a Biogen Idec Alternate Modality Product-by-Biogen Idec Alternate Modality Product basis, if, at any time during the Term, a Change of Control occurs involving Isis and a Person

that, at the time of the closing of such Change of Control, is developing in human clinical trials or commercializing a Directly Competitive Biogen Idec Alternate Modality Product within the Field or is engaged in a Directly Competitive Biogen Idec Alternate Modality Program or, at any time during the Term after such closing of the Change of Control, develops or acquires a Directly Competitive Biogen Idec Alternate Modality Product or begins a Directly Competitive Biogen Idec Alternate Modality Program (such Person being hereinafter referred to as a "***Competing Alternate Modality Acquirer***") and such Competing Alternate Modality Acquirer has not, within [***] of either (i) closing of the Change of Control in the event the Directly Competitive Alternate Product is being developed in human clinical trials or commercialized, or the Directly Competitive Alternate Modality Program exists, as of such closing date or (ii) the date of first development or acquisition of such Directly Competitive Biogen Idec Alternate Modality Product or the date on which such Competing Alternate Modality Acquirer begins such Directly Competitive Biogen Idec Alternate Modality Program (the "***Alternate Modality Divestiture Period***") divested itself of the Directly Competitive Biogen Idec Alternate Modality Product or Directly Competitive Biogen Idec Alternate Modality Program, terminated development and commercialization of such Directly Competitive Biogen Idec Alternate Modality Product or such Biogen Idec Alternate Modality Program or assigned this Agreement pursuant to Section 12.4 to a Third Party that is not itself developing or commercializing a Directly Competitive Collaboration Product or engaged in a Directly Competitive Biogen Idec Alternate Modality Program, then (i) Isis will provide written notice to Biogen Idec of the closing of such Change of Control or Alternate Modality Divestiture Period, as applicable, and (ii) [***].

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: 866-795-0181
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. For the avoidance of doubt, this Agreement in no way supersedes, modifies or otherwise affects any of the Isis/Biogen Idec Preexisting Development Agreements, which will remain in full force and effect in accordance with each of their respective terms. 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 and good laboratory and clinical practices and cGMP 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/ George Scangos*
Name: George Scangos
Title: Chief Executive Officer

SIGNATURE PAGE TO NEUROLOGY DRUG DISCOVERY AND DEVELOPMENT COLLABORATION, 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

SIGNATURE PAGE TO NEUROLOGY DRUG DISCOVERY AND DEVELOPMENT COLLABORATION, OPTION AND LICENSE AGREEMENT

List of Appendices and Schedules

APPENDIX 1

DEFINITIONS

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

"***Accelerated Target***" has the meaning set forth in Section 1.8.4.

"***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.

"***Actual Biogen Idec-Approved Costs***" has the meaning set forth in Section 1.14.5.

"***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 Plan Costs***" means [***].

"***Advisory Panel***" has the meaning in SCHEDULE 10.4.5(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 1.17.6.

"***ALS"*** means the disease amyotrophic lateral sclerosis.

"***ALS Collaboration Program***" means a Collaboration Program focused on an ALS Target.

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

"***ALS Pre-Licensing Milestone Event***" has the meaning set forth in Section 6.5.

"***ALS Target***" means the initial ALS-associated High Interest Targets identified as ALS Targets on SCHEDULE 1.2.3(a) on the Effective date, plus any ALS-associated High Interest Target that is designated as an ALS Target in accordance with Section 1.2.3(a).

"***ALS Target List***" means the list of ALS-associated High Interest Targets identified as ALS Targets on the High Interest Target List. For clarity, at any given time, if a gene target is not on the ALS Target List at such time, then such gene target is not an ALS Target.

"***Alternate Modality***" means a therapeutic approach for a gene target that is not an oligonucleotide approach.

"***Alternate Modality Divestiture Period***" has the meaning set forth in Section 12.5.4.

"***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 a Collaboration 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 a Product in any regulatory jurisdiction, approval from the applicable Regulatory Authority sufficient for the manufacture, distribution, use, marketing and sale of such 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 such Product in the marketplace, Approval will not be deemed to have occurred if the final approval to market and sell such 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 such 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 an 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, excluding any double stranded oligonucleotide compounds that are designed to act through the RNA-induced silencing complex.

"***ASO Development Candidate Identification Plan***" has the meaning set forth in Section 1.10.1(a).

"***ASO Development Candidate Identification Term***" has the meaning set forth in Section 1.10.1(b).

"***Audit Report***" has the meaning set forth in Section 6.15.

"***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 Activities***" means, under any Neurology Plan, any and all research, pre-clinical and/or clinical activities that Biogen Idec agrees to conduct; *provided* that Biogen Idec will be deemed to have agreed to conduct any activities designated as Biogen Idec Activities under any Neurology Plan it approves.

"***Biogen Idec Alternate Modality Milestone Event***" has the meaning set forth in Section 6.3.

"***Biogen Idec Alternate Modality Product***" means a finished drug product that contains a molecule that is (i) not an oligonucleotide, (ii) designed to bind, mimic or otherwise affect a protein or RNA that is encoded by a Biogen Idec Alternate Modality Target, and (iii) discovered by Biogen Idec or its Affiliates or any Third Party acting on their behalf.

"***Biogen Idec Alternate Modality Program***" means a program to discover, Develop, Manufacture and Commercialize a Biogen Idec Alternate Modality Product.

"***Biogen Idec Alternate Modality Royalty***" has the meaning set forth in Section 6.9.1.

"***Biogen Idec Alternate Modality Royalty Period***" has the meaning set forth in Section 6.9.2.

"***Biogen Idec Alternate Modality Target***" is either (i) a High Interest Target that is designated as a Biogen Idec Alternative Modality Target under Section 1.3, Section 1.4 or Section 1.8, (ii) a Collaboration Target that is changed to a Biogen Idec Alternate Modality Target under Section 3.2.2, or (v) a Collaboration Target that is added as a Biogen Idec Alternate Modality Target under Section 3.2.4.2.

"***Biogen Idec-Approved Changes***" means any changes (including number of subjects, duration of dosing, additional studies, additional endpoints, additional analysis, etc.) to the applicable Neurology Plan for a Product that are requested by either Party after the Parties have set the initial Cost Estimates for such

Neurology Plan under Section 1.10.2(e), and (i) required by a Regulatory Authority or (ii) agreed to be paid for by Biogen Idec.

"***Biogen Idec-Approved Costs***" has the meaning set forth in Section 1.14

"***Biogen Idec's FTE***" 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 6.10.1.

"***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 7.2.5(b).

"***Biogen Idec Reduced Royalty***" has the meaning set forth in Section 6.10.2(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 a Product.

"***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 2013, the Effective Date) and ending on December 31.

"***Carryover Development Candidate***" has the meaning set forth in Section 1.10.1(d).

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

"***Change of Control***" means, with respect to Isis, (a) a merger or consolidation of Isis with a Third Party which results in the voting securities of Isis 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 Isis' outstanding securities, (c) the sale or other transfer to a Third Party of all or substantially all of Isis' business to which the subject matter of this Agreement relates, or (d) the stockholders or equity holders of Isis will approve a plan of complete liquidation of Isis or an agreement for the sale or disposition by Isis of all or a substantial portion of its 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 Collaboration Product for use in a Clinical Study.

"***CMO***" means a Third Party contract manufacturer Manufacturing API, Clinical Supplies or Finished Drug Product for any purpose under this Agreement.

"***Collaboration***" means the conduct of the Neurology Plans in accordance with this Agreement.

"***Collaboration Divestiture Period***" has the meaning set forth in Section 12.5.2.

"***Collaboration Product***" means, on a Collaboration Program-by-Collaboration Program basis, a finished drug product containing a Compound as an active pharmaceutical ingredient.

"***Collaboration Program***" has the meaning set forth in Section 1.6.1.

"***Collaboration Target***" means a gene target for which the Parties wish to start an ASO drug discovery program that is either (i) a High Interest Target that is not an ALS Target and is designated as a Collaboration Target under Section 1.3 or Section 1.8, (ii) an ALS Target designated as a Collaboration Target under Section 1.5, (iii) an Isis Neurology Target designated as a Collaboration Target under Section 1.4, (iv) a Biogen Idec Alternate Modality Target that is changed to a Collaboration Target under Section 3.2.1, or (v) a Neurology Target that is added as a Collaboration Target under Section 3.2.4.1. As of the Effective Date [***] is a Collaboration Target that is an ALS Target and is not a Multi-Indication Target.

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

"***Commercialize***," "***Commercialization***" or "***Commercializing***" means any and all activities directed to marketing, promoting, detailing, distributing, importing, having imported, exporting, having exported, selling or offering to sell a Product following receipt of Approval for such 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 such Product in each country.

"***Commercializing Party***" means (a) Biogen Idec, with respect to a 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 Collaboration 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 a Product hereunder includes the use of Commercially Reasonable Efforts to perform (i) any Biogen Idec Activities in a Neurology Plan, and (ii) the "*General Activities*" described in SCHEDULE 5.1.4, and Commercially Reasonable Efforts as it applies to Isis' Development of a Product hereunder includes use of Commercially Reasonable Efforts to adhere to the activities and timelines set forth in each Neurology Plan.

"***Competing Alternate Modality Acquirer***" has the meaning set forth in Section 12.5.4.

"***Competing Collaboration Acquirer***" has the meaning set forth in Section 12.5.2.

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

"***Compound***" means, on a Collaboration Program-by-Collaboration Program basis, any ASO that is designed to bind to the RNA that encodes the applicable Collaboration Target, where such ASO is discovered by Isis prior to or in the performance of any Neurology Plan, including each Development Candidate under such Collaboration Program.

"***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 7.2.5(c).

"***Contracting Party***" has the meaning set forth in Section 1.10.7.

"***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.

"***Core Research Plan***" has the meaning set forth in Section 1.2.

"***Core Research Program***" has the meaning set forth in Section 1.2.

"***Cost Estimate***" has the meaning set forth in Section 1.10.2(e).

"***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).

"***CSC***" has the meaning set forth in Section 1.17.1.

"***CTD***" has the meaning set forth in Section 4.5.

"***Deferral Notice***" has the meaning set forth in Section 1.8.1.

"***Deferral Period***" has the meaning set forth in Section 1.8.1.

"***Deferred Target***" has the meaning set forth in Section 1.8.1.

"***Deferred Target Development Candidate"*** means a Development Candidate identified in accordance with Section 1.8.4.

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

"***Design Notice***" has the meaning set forth in Section 6.2.1.

"***Develop***," "***Developing***" or "***Development***" means with respect to a 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; *provided however* that with respect to any Primarily Neuro Multi-Indication Target, such Compound will be reasonably selected by Biogen Idec (giving good faith consideration to the input of Isis' representatives on the Neurology JRC) as a Development Candidate from the body of work Isis used to determine the applicable Compound Isis believes is 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 2.

"***Development Candidate Data Package***" means, with respect to a [***], the [***]; *provided* such package contains [***]. The checklist Isis uses as of the Effective Date when reviewing potential development candidates for approval is attached hereto as APPENDIX 2.

"***Diagnostic Option***" has the meaning set forth in Section 3.3.1.

"***Directly Competing Development Activities***" has the meaning set forth in Section 12.5.3.

"***Directly Competitive Biogen Idec Alternate Modality Product***" means with respect to a Biogen Idec Alternate Modality Product, a product designed to bind to or directly modulate the Biogen Idec Alternate Modality Target targeted by such Biogen Idec Alternate Modality Program.

"***Directly Competitive Biogen Idec Alternate Modality Program***" means any internal research program for which [***] or [***], with the goal of discovering and developing a Directly Competitive Biogen Idec Alternate Modality Product for which drug discovery activities have been initiated.

"***Directly Competitive Collaboration Product***" means with respect to a Collaboration Product, any product, other than such Collaboration Product, that is designed to bind to or directly modulate the Collaboration Target targeted by such Collaboration Product.

"***Directly Competitive Collaboration Program***" means any internal research program for which [***] or [***], with the goal of discovering and developing a Directly Competitive Collaboration Product for which drug discovery activities have been initiated.

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

"***Discontinued Collaboration Product***" means a Collaboration Product that is the subject of a termination under 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.

"***DMPK Agreement***" means the DMPK Research, Development, Option and License Agreement between the Parties dated June 27, 2012.

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

"***Drug Development Program***" means the aggregate drug development activities related to each Development Candidate through completion of the first Phase 2 PoC Trial under a Collaboration Program in accordance with the applicable Initial Development Plan for all Collaboration Programs under this Agreement.

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

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

"***Equal Multi-Indication Target***" has the meaning set forth in APPENDIX 3.

"***Estimated Biogen Idec-Approved Costs***" means Isis' good faith estimate of the Biogen Idec-Approved Costs it will incur during the applicable Measurement Period.

"***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 Collaboration Product or Deferred Target Development Candidate; (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.

"[****]" means any form of the [***].

"[******] Collaboration Program***" means an [***] Collaboration Program solely and exclusively focused on [***].

"***Field***" means, except as may be limited under Section 4.1.4, the prophylactic or therapeutic use or form of administration of a Product for any indication.

"***Finished Drug Product***" means any drug product containing API as an active ingredient in finished bulk form for the Development or Commercialization by a Party under this Agreement.

"***First Commercial Sale***" means with respect to a Product, the first sale of such 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 2.2.1.

"***Follow-On Compound***" means, with respect to a given Compound for a given Collaboration Target, any ASO (other than the Development Candidate for such Collaboration Target) that is designed to bind to the RNA that encodes such Collaboration Target discovered by or on behalf of Isis following exercise of the applicable Option by Biogen Idec.

"***Follow-On Interest Notice***" has the meaning set forth in Section 2.2.1.

"***Follow-On Negotiation Notice***" has the meaning set forth in Section 2.2.1.

"***FSHD***" means the disease facioscapulohumeral muscular dystrophy.

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

"***FTD***" means the disease frontotemporal dementia.

"***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 Costs***" has the meaning set forth in Section 1.14.

"***FTE Rate***" means $[***] for the Calendar Year 2013. The FTE Rate will be increased each Calendar Year thereafter by the [***].

"***Full Royalty Period***" has the meaning set forth in Section 6.10.2(a).

"***Fully Absorbed Cost of Goods***" means the costs incurred by Isis as determined using the methodology set forth in SCHEDULE 4.7.3 fairly applied and as employed on a consistent basis throughout Isis' operations.

"***Generic Product***" means, with respect to a particular Collaboration Product, one or more Third Party product(s) (i) having the same active pharmaceutical ingredient as such Collaboration Product and for which in the U.S. an ANDA has been filed naming such Collaboration Product as the reference listed drug or outside of the U.S., an equivalent process where bioequivalence to such Collaboration 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 such Collaboration 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.

"***High Interest Target***" has the meaning set forth in Section 1.2.3(a). For clarity, at any given time, if a gene target is not on the High Interest Target List at such time, then such gene target is not a High Interest Target.

"***High Interest Target List***" has the meaning set forth in Section 1.2.3(a).

"***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.

"***Initial Development Plan***" has the meaning set forth in Section 1.10.2(d).

"***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 5.1.6.

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

"***Isis Activities***" means the research, pre-clinical and/or clinical activities for which Isis is designated as responsible under any Neurology Plan.

"***Isis/Biogen Idec Preexisting Development Agreements***" means the (i) SMN Agreement, (ii) DMPK Agreement, and (iii) Neurology Drug Discovery and Development Collaboration, Option and License Agreement entered into by the Parties dated December 10, 2012 (as such agreements may be amended by the Parties).

"***Isis Breach Event***" has the meaning set forth in Section 10.4.5(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 8.2.4(a) attached hereto.

"***Isis In-License Agreements***" has the meaning set forth in Section 6.13.1(a).

"***Isis Internal ASO Safety Database***" has the meaning set forth in Section 5.2.7.

"***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 a 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 a 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 they related to ASOs as of the Effective Date is set forth on SCHEDULE 8.2.4(b) attached hereto. Isis Manufacturing and Analytical Patents do not include the Isis Product-Specific Patents or the Isis Core Technology Patents.

"***Isis Multi-Indication Compound***" has the meaning set forth in APPENDIX 3.

"***Isis Neurology Target***" means a Neurology Target that (1) is not (i) a High Interest Target for which target validating activities are planned under the then-current Neurological Disease Research Plan, (ii) an ALS Target, (iii) a Collaboration Target, or (iv) a Biogen Idec Alternate Modality Target and (2) has a Neurological Disease as its primary disease association.

"***Isis Non-Exclusive Product***" has the meaning set forth in Section 2.1.1(c).

"***Isis Platform Technology***" has the meaning set forth in Section 8.2.4.

"***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 8.2.4(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.

"***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. For clarity, Licensed Patents that are jointly-owned by Isis and Biogen Idec will count toward the calculation of the Full Royalty Period in a particular country if the use or sale of a Product by an unauthorized Third Party in such country would infringe a Valid Claim of such Licensed Patent.

"***Licensed Technology***" means, on a Product-by-Product basis, 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 such Product. Licensed Technology does not include any technology in-licensed by Isis from [***] under the [***]

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

"***MAA***" means, with respect to a particular Product, a marketing authorization application filed with the EMA after completion of Clinical Studies to obtain Approval for such 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, with respect to a particular Product, the Approval of an MAA by the EMA for such 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 bulk active pharmaceutical ingredient for a Biogen Idec Alternate Modality Product, or a Collaboration Product or Biogen Idec Alternate Modality Product in finished form.

"***Measurement Period***" has the meaning set forth in Section 1.14.3 or Section 1.14.4, as applicable.

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

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

["***"] means a disease that has, as its [***]

"***Multi-Indication Target***" has the meaning set forth in Section 1.2.3(b).

"***Multi-Indication Target Notice***" has the meaning set forth in Section 1.2.3(b).

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

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

"***Negotiation Period***" has the meaning set forth in Section 2.2.2.

"***Net Sales***" means the gross amount billed or invoiced on sales of a 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 such 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 a Product between Biogen Idec, its Affiliates and Sublicensees, Net Sales are calculated based on the final sale of such Product to an independent Third Party. If Biogen Idec, its Affiliate or a Sublicensee receives non-monetary consideration for a 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 a 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 will 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.

With respect to Net Sales as it applies to royalties payable by Isis, the Parties agree that any reasonable definition of "net sales" that is (x) customarily used in pharmaceutical industry technology licensing or collaboration contracts and (y) consistent with generally accepted accounting principles in the United States ("***GAAP***") or International Financial Reporting Standards and is subsequently agreed to by Isis (or a Third Party acquirer or assignee) and Isis' sublicensee or commercialization partner in an arms-length transaction under a particular sublicense or commercialization agreement will replace the definition of Net Sales in this Agreement and will be used in calculating the royalty payment to Biogen Idec on sales of products sold pursuant to such agreement. If Isis uses such an alternate definition of "net sales" in a particular sublicense, (A) Isis will include such "net sales" definition in the applicable royalty reports to assist Biogen Idec with verifying royalty payments and (B) if such definition is not consistent with GAAP or International Financial Reporting Standards, upon Biogen Idec's request, Isis will reconcile the royalties calculated under such definition with GAAP or International Financial Reporting Standards.

"***Neurological Disease Research Plan***" has the meaning set forth in Section 1.2.

"***Neurological Disease Research Program***" has the meaning set forth in Section 1.2.

"***Neurology JDC***" has the meaning set forth in Section 1.17.3.

"***Neurology JRC***" has the meaning set forth in Section 1.17.2.

"***Neurology Plan***" means any of the following plans: (i) the Core Research Plan, (ii) the Neurological Disease Research Plan, (iii) any ASO Development Candidate Identification Plans, or (iv) any Initial Development Plans.

"***Neurology Target***" means any gene target that (i) as of the Effective Date, (y) has not been encumbered by Isis under an agreement with a Third Party that would prevent Isis from granting Biogen Idec the license under Section 4.1.1 of this Agreement with respect to such gene target, and (z) has not yet achieved Target Sanction status, and (ii) as of the Effective Date or during the Research Term, the expression or activity of the gene in neurons is demonstrated to have an association to any one of the following (each of (a) through (e) below, a "***Neurological Disease***"):

[***]

For purposes of clarity, [***] are expressly excluded from the above-listed [***] and therefore any gene target that has as its primary disease association an association to [***] will not be a Neurology Target, and any [***] will not be a Product under this Agreement. In addition, [***] or [***] are expressly

excluded from the above-listed [***] and therefore any gene target that has as its [***] will not be a Neurology Target. For purposes of further clarity, a gene target that has as its [***] would not be considered a Neurology Target.

"***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.

"***Non-Neurological Indications***" means therapeutic uses that are not designed to treat neurological diseases or [***] diseases.

[***] means diseases that have, as their [***]

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

"***Option Acceleration Deadline***" has the meaning set forth in Section 1.10.2(g).

"***Option Acceleration Notice***" has the meaning set forth in Section 1.10.2(g).

"Option Deadline" means the Standard Option Deadline or ALS Option Deadline, as applicable.

"***Option Period***" means, with respect to a Collaboration Program, the period beginning on the date a Neurology Target is designated a Collaboration Target hereunder and ending on the expiration or earlier termination of the Option with respect to such Collaboration Program.

"***Panel Decision***" has the meaning set forth in Section 10.4.5(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 non-commercial 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 5.2.2.

"***Phase 1 Trial***" means the first clinical study in human beings Initiated by Isis or Biogen Idec under the applicable Initial Development 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 for a given Development Candidate, then the definition of ***"Phase 1 Trial"*** means the first clinical study of the applicable Development Candidate in human beings Initiated by Biogen Idec, its Affiliate or its Sublicensee.

"***Phase 1 Trial Design***" means, with respect to a Collaboration Program, the Phase 1 Trial design set forth in the applicable Initial Development 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 Neurology JDC).

"***Phase 2 Trial***" means, with respect to a Product, 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 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, with respect to a 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, with respect to a Product, (a) any Clinical Study conducted to satisfy a requirement of a Regulatory Authority in order to maintain a Regulatory Approval for such Product or (b) any Clinical Study conducted after the first Regulatory Approval in the same disease state for which such Product received Regulatory Approval other than for purposes of obtaining Regulatory Approval.

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

"***PoC Trial***" means, with respect to a Collaboration Program, the first phase 2a Clinical Study in human patients with a pharmacokinetic or target reduction endpoint or other therapeutic or physiological endpoint.

"***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 each Initial Development 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 Neurology JDC).

"***Post-Licensing Milestone Event***" means either a Standard Post-Licensing Milestone Event or an ALS Post-Licensing Milestone Event, as applicable.

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

*"**Pre-Existing Target**"* has the meaning set forth in Section 1.2.3(c).

"***Pre-Licensing Milestone Event***" means an ALS Pre-Licensing Milestone Event or a Standard Pre-Licensing Milestone Event, as applicable.

"***Primarily Neuro Multi-Indication Target***" has the meaning set forth in APPENDIX 3.

"***Primarily Other Multi-Indication Target***" has the meaning set forth in APPENDIX 3.

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

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

"***Product***" means (i) a Biogen Idec Alternate Modality Product, or (ii) a Collaboration Product.

"***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 a Collaboration Product, or (ii) methods of using a 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 or products in general, or (z) include an ASO, the sequence of which targets the RNA that encodes a Collaboration Target and the RNA of a gene that does not encode a Collaboration Target (or similarly, a non-ASO molecule that binds, mimics or otherwise affects a protein or RNA that is encoded by a Biogen Idec Alternate Modality Target and the RNA of a gene that does not encode a Biogen Idec Alternate Modality Target), 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.

[***] means a [***]

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

"***Reduced Royalty Period***" has the meaning set forth in Section 6.10.2(d).

"***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 a Product in any country.

"***Research***" means conducting the research activities with ASOs or Compounds as set forth in the Research Plan or each ASO Development Candidate Identification 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.

"***Research Term***" has the meaning set forth in Section 1.2.1.

"***Reverse Royalties***" has the meaning set forth in Section 6.12.1.

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

"***ROFN Period***" has the meaning set forth in Section 2.2.

"***ROFN Termination Event***" has the meaning set forth in Section 2.2.1.

"***Royalty Quotient***" has the meaning set forth in Section 6.10.2(c).

"***Service Provider***" means the Third Party(ies) conducting the original and revised studies under the applicable Initial Development Plan.

"***Setoff Amount***" has the meaning set forth in Section 10.4.5(b).

"***Setoff Dispute***" has the meaning set forth in Section 10.4.5(b).

"***Setoff Dispute Notice***" has the meaning set forth in Section 10.4.5(b).

"***SMN Agreement***" means the Development, Option and License Agreement between the Parties dated January 3, 2012.

"***Specific Performance Milestone Events***" has the meaning set forth in Section 5.1.4.

[***] means the form of the [***].

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

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

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

"***Superior Patent Right***" has the meaning set forth in Section 7.2.5(c).

"***Target Related Biogen Idec Program Claim***" has the meaning set forth in Section 4.4.3.

"***Target Related Isis Program Claim***" has the meaning set forth in Section 4.4.2.

"***Target Sanction***" means when the therapeutic potential of a Neurology Target has been demonstrated in pre-clinical disease models and such Neurology Target has received approval by Isis' RMC to justify expending resources to identify a human Development Candidate, all in accordance with Isis' standard processes.

"***Target Sanction Data Package***" means, with respect to a Neurology Target, the data package Isis presented to its RMC to obtain approval to justify expending resources to identify a human Development Candidate, all in accordance with Isis' standard processes; *provided* such package contains the same level of detail as the data packages Isis currently presents to its Research Management Committee to approve Isis' own internal gene targets.

"***Technical Failure***" has the meaning set forth in Section 1.10.1(b).

"***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 a Product, Biogen Idec Alternate Modality Target or a Collaboration Target, 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 10.4.5(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

Development Candidate Checklist

[***]

APPENDIX 3

Multi-Indication Target Process

Neurology Targets with Broader Therapeutic Benefit.

(a) If, pursuant to Section 1.2.3(d), the CSC is unable to agree upon whether a Multi-Indication Target is a Primarily Neuro Multi-Indication Target, Equal Multi-Indication Target or Primarily Other Multi-Indication Target, the Parties will engage an expert panel under Section 12.1.4 to make such determination. Such expert panel will first determine the net present value ("***NPV***") of a therapeutic targeting such Multi-Indication Target and allocate such NPV between the markets for Neurological Disease indications and for Non-Neurological Indications, where such NPV calculations and allocations will take into consideration, and risk-adjust for, the relevant market sizes, competitive landscapes, scientific rationale for each market and any other factors deemed relevant by such expert panel. Based on such NPV calculations and allocations, Multi-Indication Targets will be classified as either ***"Primarily Neuro Multi-Indication Targets"***; ***"Equal Multi-Indication Targets"*** or ***"Primarily Other Multi-Indication Targets"***, where (1) a Multi-Indication Target with [***]% or more of its NPV allocated to the market for Neurological Disease indications will be a Primarily Neuro Multi-Indication Target, (2) a Multi-Indication Target with less than [***]% but more than [***]% of its NPV allocated to the market for Neurological Disease indications will be an Equal Multi-Indication Target, and (3) a Multi-Indication Target with [***]% or less of its NPV allocated to the market for Neurological Disease indications will be Primarily Other Multi-Indication Target.

(b) **Primarily Neuro Multi-Indication Targets**. If a Multi-Indication Target is classified as a Primarily Neuro Multi-Indication Target, then within [***] days of such classification, Biogen Idec will send Isis a written notice either (1) electing to negotiate in good faith with Isis a development plan and [***] (i.e., [***]) for the Non-Neurological Indications if Developed and Commercialized under this Agreement, which plan and provisions will be recommended to the CSC for approval; (2) granting Isis and its Affiliates the right to work on their own or with a Third Party to discover, develop and commercialize an oligonucleotide against such Multi-Indication Target for primarily Non-Neurological Indications (an "***Isis Multi-Indication Compound***"); or (3) precluding Isis and its Affiliates from working on their own or with a Third Party to discover, develop commercialize an Isis Multi-Indication Compound. If under this Section (c) Isis or any of its Affiliates or licensees Commercializes a product incorporating an Isis Multi-

Indication Compound, and Biogen Idec has paid the applicable License fee under Section 6.6 for the applicable Collaboration Program, then until the earlier of (i) the [***] anniversary of the date of First Commercial Sale of such product or (ii) the date Biogen Idec, its Affiliates and sublicensees stop Commercializing the Product related to such Multi-Indication Target, Isis will pay Biogen Idec a royalty of [***]% of Annual worldwide Net Sales of such product sold by Isis, its Affiliates or Sublicensees. The definition of Net Sales in APPENDIX 1 and the other provisions contained in Sections 6.14, 6.15, 6.16, and 6.17 governing payment of royalties from Biogen Idec to Isis will govern the payment of such royalty from Isis to Biogen Idec under this Section (c), *mutatis mutandis*. If within [***] days of Biogen Idec making an election under clause (1) of this Section (c) to pursue the Non-Neurological Disease indication, the CSC has not agreed on a development plan and enhanced economic provisions to be paid by Biogen Idec for the Non-Neurological Indication, then (I) Isis and its Affiliates will not work on their own or with a Third Party to discover, develop and commercialize in the Field an Isis Multi-Indication Compound unless otherwise permitted under this Agreement and (II) Biogen Idec and its Affiliates will not work on their own or with a Third Party to discover, develop or commercialize Compounds related to such Multi-Indication Target for Non-Neurological Indications.

(c) **Equal Multi-Indication Targets**. If a Multi-Indication Target is classified as an Equal Multi-Indication Target, neither Party nor its respective Affiliates, licensees or sublicensees may develop or commercialize a product targeting such Multi-Indication Target for any indication unless and until Isis and Biogen Idec have agreed on (i) a development plan and enhanced economic provisions to be paid by Biogen Idec (i.e., multi-indication filing and approval milestone payments, but not additional license fees) for the Non-Neurological Indications, and (ii) the restrictions under which Isis or Biogen Idec (as applicable) would develop or commercialize a product targeting such Multi-Indication Target (which terms may include the requirements set forth under clause (d)(2) below).

(d) **Primarily Other Multi-Indication Targets**. If a Multi-Indication Target is classified as a Primarily Other Multi-Indication Target, then (A) Biogen Idec may continue to Develop and Commercialize Products for Neurological Disease indications pursuant to the terms of this Agreement, and (B) within [***] days of such classification, Biogen Idec will send Isis a written notice either (1) electing to negotiate in good faith with Isis and agree on a development plan and [***] (i.e., [***]) for the Non-

Neurological Indications if Developed and Commercialized under this Agreement, which plan and provisions will be recommended to the CSC for approval; or (2) granting Isis and its

Affiliates the right to work on their own or with a Third Party to discover, develop and commercialize an Isis Multi-Indication Compound so long as such Isis Multi-Indication Compound [***], *provided*, in addition to the foregoing provisions, if the Development Candidate targeting such Multi-Indication Target being Developed or Commercialized by Biogen Idec, its Affiliates or Sublicensees under this Agreement is [***], Isis cannot develop or commercialize such Isis Multi-Indication Compound for [***].

(e) If within [***] days of Biogen Idec making an election under clause (B)(1) of Section (e) of this APPENDIX 3 to pursue the Non-Neurological Indication, the CSC has not agreed on a development plan and [***] (i.e., [***]) for the Non-Neurological Indications, then Isis and its Affiliates will have the right to work on their own or with a Third Party to discover, develop and commercialize an Isis Multi-Indication Compound so long as such Isis Multi-Indication Compound [***].

SCHEDULE 1.2.4

Terms and Conditions for Provision of Research ASOs to Biogen Idec

ARTICLE 1
DEFINITIONS

The terms used in this SCHEDULE 1.2.4 with initial letters capitalized, whether used in the singular or the plural, will have the meaning set forth in ATTACHMENT 1, or if not listed in ATTACHMENT 1, the meaning designated in places throughout the Agreement (or APPENDIX 1 to the Agreement).

ARTICLE 2
PROVISION OF RESEARCH ASOS OUTSIDE OF THE DISEASE RESEARCH PROGRAM

2.1 Scope of Collaboration.

a) Isis will generate Research ASOs for Accepted Gene Targets in accordance with the terms and conditions of this SCHEDULE 1.2.4.

b) Each Party will devote commercially reasonable efforts to performing its obligations under the Target Validation Plan.

ARTICLE 3
CONDUCT OF THE TARGET VALIDATION OUTSIDE OF THE DISEASE RESEARCH PROGRAM

3.1. Selection of Biogen Idec TV Targets; Target Validation Activities.

a) During the Research Term, Biogen Idec will have the right to propose Biogen Idec TV Targets for up to a total of [***] Accepted Gene Targets per [***] period. Biogen Idec will propose such Biogen Idec TV Targets by written notice to the Isis Alliance Manager.

b) Isis may reject a proposed Biogen Idec TV Target if, at the time of such proposal, [***].

c) Each Biogen Idec TV Target that is not rejected by Isis will be an "***Accepted Gene Target.***" During the Research Term, Isis and Biogen Idec will use Commercially Reasonable Efforts to perform the activities outlined in the Target Validation Plan on each Accepted Gene Target.

3.2 Biogen Idec' Use of Research ASOs and Information.

a) The Research ASOs and any related Confidential Information provided to Biogen Idec by Isis hereunder are proprietary to Isis. Biogen Idec will not distribute or release the Research ASOs to any person other than its employees, academic collaborators, Affiliates, agents or (sub)contractors, solely for purposes of performing work in support of Biogen Idec's drug discovery activities. Subject to the terms and conditions of this SCHEDULE 1.2.4, Isis hereby grants Biogen Idec a non-exclusive, fully paid, license to use the Isis Confidential Information (including data generated by Isis with Research ASOs in the performance of the Target Validation Plan) and Research ASOs solely for use in support of Biogen Idec' drug discovery

purposes. In exercising its rights under this SCHEDULE 1.2.4, Biogen Idec may use data generated by Biogen Idec using the Research ASOs (the "***Biogen Idec Data***") to support Patent Rights filed by or on behalf of Biogen Idec, including Patent Rights that claim methods of treating disease by modulating the applicable Accepted Gene Target. The claims of any such Biogen Idec Patent Right using such Biogen Idec Data that generically claims methods of treating disease by modulating the applicable Accepted Gene Target, but are not directed to specific compounds or agents, are referred to as the "***Biogen Idec Licensed Claims***." Notwithstanding the foregoing, Biogen Idec will not use such Biogen Idec Data to support claims directed to one or more oligonucleotides as a composition of matter or one or more oligonucleotides as a pharmaceutical product, without the prior written consent of Isis. In addition, Biogen Idec may not use Isis data disclosed to Biogen Idec in connection with this SCHEDULE 1.2.4 or the Research ASOs to make products that incorporate oligonucleotides.

b) Biogen Idec hereby grants Isis a non-exclusive, fully-paid sublicensable license under any Biogen Idec Licensed Claims solely for the purpose of discovering, developing or commercializing an oligonucleotide(s) as a pharmaceutical product, *provided however*, that such license will only be sublicensable by Isis to a Third Party licensee in connection with the grant of an exclusive license to such Third Party under other Isis intellectual property with respect to such oligonucleotide. No other license is granted to Isis under any Biogen Idec-owned or controlled Patent Right or other intellectual property under this SCHEDULE 1.2.4. For avoidance of doubt, no rights are granted by Biogen Idec to Isis under this SCHEDULE 1.2.4 (expressly or by implication or otherwise) with respect to any compounds, materials or agents (or any method of use or manufacture thereof).

c) Isis hereby grants Biogen Idec a non-exclusive, fully-paid sublicensable license under any Isis Licensed Claims solely for the purpose of discovering, developing or commercializing a non-oligonucleotide compound(s) as a pharmaceutical product, *provided however*, that such license will only be sublicensable by Biogen Idec to a Third Party licensee in connection with the grant of an exclusive license to such Third Party under other Biogen Idec intellectual property with respect to any such non-oligonucleotide compound. "***Isis Licensed Claims***" means the claims of any Isis Invention that generically claims methods of treating disease by modulating an Accepted Gene Target, but are not directed to any specific compound or agent (including any oligonucleotide). Except as set forth in Section 3.2(a) and (c), no other license is granted to Biogen Idec under any Isis-owned or controlled Patent Right or other intellectual property under this SCHEDULE 1.2.4.

3.3. Non-exclusive Collaboration.

a) Isis will perform target validation activities and will provide Research ASOs to Biogen Idec as set forth in the Target Validation Plan on a non-exclusive basis. Isis may collaborate with Third Parties for target validation studies on any gene targets, including Accepted Gene Targets. In addition, this SCHEDULE 1.2.4 will not limit Isis from conducting research, discovery and development work on any and all oligonucleotides, for itself or with or on behalf of a Third Party.

b) If an oligonucleotide to an Accepted Gene Target hereunder becomes a drug development candidate of Isis or a Third Party collaborator of Isis, Isis will notify Biogen Idec. Upon receipt of such notice from Isis, Biogen Idec will return to Isis all unused quantities of applicable TV Compound within [***] days after the date on which Biogen Idec received such notice. After such time, Isis will not have any obligation to provide additional quantities of the originally supplied TV Compound to Biogen Idec under this SCHEDULE 1.2.4.

c) If Isis achieves Target Sanction for an Accepted Gene Target, and Isis does not at such time have any obligations to any Third Party with respect to such Accepted Gene Target that would conflict with Isis' compliance with this Section 3.3(c), Isis will provide to Biogen Idec a Target Sanction Data Package for such Accepted Gene Target (an "***AGT Target Sanction Data Package***") and Biogen Idec will have [***] days following receipt of such AGT Target Sanction Data Package to decide whether to negotiate with Isis regarding an agreement with respect to such Accepted Gene Target (an "***AGT Agreement***"). Following delivery of an AGT Target Sanction Data Package, Isis will not initiate negotiations regarding or enter into an AGT Agreement with any Third Party until the earlier to occur of: (1) Biogen Idec notifying Isis that it declines the opportunity to negotiate with Isis regarding such AGT Agreement; (2) Biogen Idec not responding to Isis within 30 days after receipt of such AGT Target Sanction Data Package; or (3) the AGT Negotiation Period expiring before Biogen Idec and Isis have entered into such AGT Agreement. If Biogen Idec or one of its Affiliates responds within [***] days after its receipt of the AGT Target Sanction Data Package indicating that Biogen Idec or one of its Affiliates desires to negotiate with Isis regarding the proposed AGT Agreement, Isis and Biogen Idec or one of its Affiliates will negotiate in good faith for 180 days thereafter (or such other period as mutually agreed by the Parties) (the "***AGT Negotiation Period***") regarding a mutually satisfactory AGT Agreement. During the AGT Negotiation Period, Biogen Idec or its Affiliate will make the first written proposal to Isis setting forth all material business and legal terms on which Biogen Idec or its Affiliate would be willing to enter into the proposed AGT Agreement with Isis; *provided, that* neither Party will have any obligation to enter into an AGT Agreement. If the AGT Negotiation Period expires before Biogen Idec or its Affiliate and Isis have entered into such AGT Agreement, Isis will have no further obligation to negotiate with Biogen Idec or its Affiliates with respect to such AGT Agreement and Isis will be free to negotiate and enter an agreement with a Third Party with respect to an AGT Agreement [***]; *provided, however*, that Isis will not enter into any such AGT Agreement with any Third Party unless the terms and pricing of such AGT Agreement, [***].

3.4. Biogen Idec Materials.

Any materials provided by Biogen Idec to Isis in connection with a Biogen Idec TV Target or Accepted Gene Target, including any biological materials with respect to screening assays, including any progeny, expression products, mutants, replicates, derivatives and modifications thereof, (such materials being individually and collectively referred to as the "***Biogen Idec Materials***") will be used by Isis solely for purposes of performing activities in accordance with the Target Validation Plan and any remaining Biogen Idec Materials will be returned to Biogen Idec (or destroyed as may be requested by Biogen Idec in writing) promptly following the end of the applicable activities under the Target Validation Plan or earlier upon request by Biogen Idec. All information related to such Biogen Idec Materials will be Biogen Idec Confidential Information. All such materials must be used with prudence and appropriate caution in any experimental work, since all of their characteristics may not be known.

ARTICLE 4
INTELLECTUAL PROPERTY

4.1. Ownership of Inventions.

a) Title to any inventions, technology, discoveries, or other proprietary property made or discovered (as determined by the U.S. laws of inventorship) by employees of or consultants or contractors of a Party pursuant to the performance Target Validation Plan (collectively, "***Inventions***") are retained by the Party that is the employer of the inventor (or, in the case of consultants or

contractors, the Party for which such consultant or contractor is providing services). Isis will own Inventions invented solely by employees or consultants or contractors of Isis and any Patent Rights claiming such Invention (collectively, the "***Isis Inventions***"). Biogen Idec will own Inventions invented solely by employees or consultants or contractors of Biogen Idec and any Patent Rights claiming such Invention (collectively, the "***Biogen Idec Inventions***").

b) Except as provided otherwise herein, Isis and Biogen Idec will jointly hold title to all Inventions, made or discovered (as determined by the U.S. laws of inventorship) jointly by employees or consultants or contractors of Isis and Biogen Idec ("***Joint Inventions***"). Patent Rights claiming such Joint Inventions will be "***Joint Patents.***" Isis and Biogen Idec will promptly provide each other with notice whenever a Joint Invention is made or discovered.

c) The Parties agree, upon reasonable request, to execute any documents reasonably necessary to effect and perfect each other's ownership of any Invention or Patent Right claiming such Invention.

4.2. Patent Prosecution; Infringement of Joint Patents.

a) Each Party has the right to file, prosecute, maintain, enforce and defend Patent Rights on Inventions owned by such Party, at its own expense.

b) Isis and Biogen Idec will mutually agree on the filing, prosecution and maintenance of any Joint Patents and the expenses of such prosecution and maintenance will be shared equally. If either Party elects not to participate in the filing, prosecution or maintenance of a Joint Patent, it will notify the other Party of such election not later than [***] days before the applicable deadline for filing, prosecution or maintenance, and the other Party will thereafter have the right to undertake such filing, prosecution or maintenance, at its own expense.

c) A Party whose rights in a Joint Patent are impacted by the infringement of such Joint Patent by a Third Party will have the right to enforce that Joint Patent at its own discretion and at its own expense. The non-enforcing Party agrees to provide the enforcing Party all reasonable assistance (including joining such action as a Party plaintiff), at the enforcing Party's expense. Any damages or other recovery, whether by settlement or otherwise, from an action hereunder to enforce a Joint Patent will be paid first to each Party to reimburse the costs of enforcement and then prorated to the Party(ies) based on damages incurred.

ARTICLE 5
TERM AND TERMINATION

5.1. Agreement Term.

Unless the Agreement is earlier terminated (in which case this SCHEDULE 1.2.4 will also terminate), this SCHEDULE 1.2.4 will remain in effect until the end of the Research Term (the "***Term***"), at which time it will expire.

5.2 Survival.

Section 3.2 (Use of Research ASOs and Information), Section 5.2 (Survival) and Article 4

(Intellectual Property) will survive the expiration or termination of this SCHEDULE 1.2.4.

ATTACHMENT 1 to SCHEDULE 1.2.4

DEFINITIONS

"***Accepted Gene Target***" has the meaning set forth in Section 3.1(c).

"***AGT Agreement***" has the meaning set forth in Section 3.3(c).

"***AGT Negotiation Period***" has the meaning set forth in Section 3.3(c).

"***AGT Target Sanction Data Package***" has the meaning set forth in Section 3.3(c).

"***Biogen Idec Data***" has the meaning set forth in Section 3.2(a).

"***Biogen Idec Inventions***" has the meaning set forth in Section 4.1(a).

"***Biogen Idec Licensed Claims***" has the meaning set forth in Section 3.2(a).

"***Biogen Idec Materials***" has the meaning set forth in Section 3.4.

"***Inventions***" has the meaning set forth in Section 4.1(a).

"***Isis Inventions***" has the meaning set forth in Section 4.1(a).

"***Isis Licensed Claims***" has the meaning set forth in Section 3.2(c).

"***Joint Invention***" has the meaning set forth in Section 4.1(b).

"***Joint Patents***" has the meaning set forth in Section 4.1(b).

"***Target Validation Plan***" means the collaborative Target Validation Plan undertaken by the Parties pursuant to this SCHEDULE 1.2.4, as further described in Attachment 2.

"***Term***" has the meaning set forth in Section 5.1.

"***TV Compound***" means an oligonucleotide delivered to Biogen Idec by Isis under this SCHEDULE 1.2.4 directed to an Accepted Gene Target.

ATTACHMENT 2 to SCHEDULE 1.2.4

TARGET VALIDATION PLAN

[***]

SCHEDULE 1.10.2(C)

Isis' Standard IND-Enabling Toxicology Studies

[***]

SCHEDULE 1.17.1

Collaboration Steering Committee Governance

CSC Representatives

Isis

Lynne Parshall, Chief Operating Officer

Frank Bennett, SVP, Head of Research

Richard Geary, SVP, Head of Development

Biogen Idec

Doug Williams, EVP, Research and Development

Steve Holtzman, EVP, Corporate Development

Amit Rakhit, VP, Program Leadership and Management

SCHEDULE 1.17.2

NEUROLOGY JRC GOVERNANCE

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

(b) The Neurology JRC may hold meetings in person or by audio or video conference as determined by the Neurology JRC; 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 Neurology JRC meetings as participating non-members. In addition, upon prior approval of the other Party, each Party may invite its employees or consultants to attend Neurology JRC meetings, including any subject matter expert(s) with valuable knowledge of High Interest Targets or Collaboration Targets (as applicable) or the diseases associated with such targets.

(c) The co-chairs will be responsible for ensuring that activities occur as set forth in this Agreement, including ensuring that Neurology JRC meetings occur, Neurology JRC recommendations are properly reflected in the minutes, and any dispute is given prompt attention and resolved in accordance with Section 1.17.2, Section 7.1.3 and Section 12.1, as applicable.

(d) The Neurology JRC members from the same Party will collectively have one vote. The Neurology JRC 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 Neurology JRC meeting.

(e) The Neurology JRC 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 Neurology JRC dissolves.

SCHEDULE 1.17.3

Neurology JDC Governance

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

(b) The Neurology JDC may hold meetings in person or by audio or video conference as determined by the Neurology JDC; 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 Neurology JDC meetings as participating non-members. In addition, upon prior approval of the other Party, each Party may invite its employees or consultants to attend Neurology JDC meetings, including any subject matter expert(s) with valuable knowledge of the applicable or Collaboration Target or the diseases associated with such target.

(c) The co-chairs will be responsible for ensuring that activities occur as set forth in this Agreement, including ensuring that Neurology JDC meetings occur, Neurology JDC recommendations are properly reflected in the minutes, and any dispute is given prompt attention and resolved in accordance with Section 1.17.3, Section 7.1.3 and Section 12.1, as applicable.

(d) Neurology JDC members from the same Party will collectively have one vote. The Neurology JDC 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 Neurology JDC meeting.

(e) The Neurology JDC 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 Neurology JDC dissolves.

SCHEDULE 1.17.6

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 Collaboration;

(c) Organizing CSC, Neurology JRC and Neurology JDC meetings, including agendas, drafting minutes, and publishing final minutes;

(d) Supporting the co-chairs of the CSC, Neurology JRC and Neurology JDC 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 CSC, Neurology JRC and Neurology JDC;

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

(g) Manage and coordinate the target validation activities under Schedule 1.2.4;

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

(i) 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; and

(j) Determining an appropriate format for summaries of resource and FTE utilization, and ensuring such summarized are timely provided to the JRC as outlined in Section 1.11.

SCHEDULE 4.7.3

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

[***]

155

SCHEDULE 5.1.4

Biogen Idec's Development and Commercialization Activities

[***]

156

SCHEDULE 6.10.2(e)

Royalty Calculation Examples

[***]

157

SCHEDULE 6.10.2(f)

Allocation of Net Sales

[***]

158

SCHEDULE 6.13.1

Certain Isis In-License Agreements

(Relevant to the High Interest Targets as of the Effective Date)

[***]

159

SCHEDULE 8.2.4(a)

Isis Core Technology Patents

[***]

160

SCHEDULE 8.2.4(b)

Isis Manufacturing and Analytical Patents

[***]

161

SCHEDULE 8.2.4(c)

Isis Product-Specific Patents

[***]

SCHEDULE 8.2.8

Prior Agreements

[***]

SCHEDULE 10.4.5(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 [***] 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

TABLE A
Applicable License Fee Payments in Change of Control for Collaboration Products

[***]

SCHEDULE 12.5

TABLE B
Applicable [***] under Section 12.5.1(b) in Change of Control

[***]

CONFIDENTIAL
EXECUTION COPY

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

AMENDMENT #1 TO COLLABORATION, LICENSE AND DEVELOPMENT AGREEMENT

This **AMENDMENT #1 TO COLLABORATION, LICENSE AND DEVELOPMENT AGREEMENT** (this "***Amendment***") is entered into as of the date of last signature hereof (the ***"Amendment 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 **ASTRAZENECA AB**, a company incorporated in Sweden under no. 556011-7482 ("***AstraZeneca***"). Isis and AstraZeneca are each referred to herein by name or as a "***Party***" or, collectively, as "***Parties***."

RECITALS

WHEREAS, Isis and AstraZeneca are parties to the Collaboration, License and Development Agreement dated December 7, 2012 (the "***Agreement***");

WHEREAS, Isis and AstraZeneca desire to amend the Agreement to add an additional research program focused on the gene target [***] (GenBank accession # [***]) or any alternative splice variants, mutants, polymorphisms and fragments thereof (the ***"Amendment-Additional Collaboration Target"***); and

NOW, THEREFORE, in consideration of the premises and mutual covenants herein contained, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, and solely with respect to the newly created program focused on the Amendment-Additional Collaboration Target, the Parties, intending to be legally bound, do hereby agree as follows:

1. **Amendment-Additional Collaboration Target Program**. In addition to the three Oncology Collaboration Programs under the Agreement, the Parties will conduct a research and development program on the Amendment-Additional Collaboration Target (the ***"Amendment-Additional Collaboration Target Program"***) in accordance with this Amendment and the plan for the research and development of the Amendment-Additional Collaboration Target (the ***"Amendment-Additional Collaboration Target Research and Development Plan"***). The initial Amendment-Additional Collaboration Target Research and Development Plan is attached hereto as ATTACHMENT 1 and sets forth the activities to be conducted by each Party to reach Target Sanction for the Amendment-Additional Collaboration Target. Once the Amendment-Additional Collaboration Target has reached Target Sanction, within [***] days the Parties will mutually agree to updates to the Amendment-Additional Collaboration Target Research and Development Plan to include the specific activities and studies under the Amendment-Additional Collaboration Target Research and Development Plan each Party

will perform to identify a Development Candidate for the Amendment-Additional Collaboration Target. This Amendment is without prejudice to AstraZeneca's rights under Section 2.2.4(b) of the Agreement to add an additional Oncology Target to the Oncology Collaboration as set out therein.

2. **Amendment-Additional Collaboration Target Rights and Obligations.** For purposes of the Agreement (except as explicitly set forth in this Amendment):

a. the Amendment-Additional Collaboration Target will be considered a Gene Target under the Agreement and will be treated the same as an Oncology Target under the Agreement, including but not limited to Article 5 of the Agreement except that in Article 5.2 of the Agreement as it applies to the Amendment-Additional Collaboration Target the references to cancer shall be read as references to [***].

b. the Amendment-Additional Collaboration Target Research and Development Plan will be treated the same as an Oncology Research and Development Plan;

c. ASOs that are designed to bind to the RNA that encodes the Amendment-Additional Collaboration Target, where such ASO is discovered by Isis prior to the Amendment Date or in the performance of the Amendment-Additional Collaboration Target Research and Development Plan (***"Amendment-Additional Collaboration Target Compounds"***) will be treated the same as Oncology Compounds; the discovery research program focused on discovering Amendment-Additional Collaboration Target Compounds to select an Amendment-Additional Collaboration Target Development Candidate in accordance with the Amendment-Additional Collaboration Target Research and Development Plan will be treated the same as an Oncology Collaboration Program;

d. An Amendment-Additional Collaboration Target Compound that is determined by Isis' RMC in accordance with Isis' standard procedures for designating development candidates as ready to start IND-Enabling Toxicology Studies, will be treated the same as a Lead Candidate;

e. A Development Candidate selected by AstraZeneca arising out of the work conducted under the Amendment-Additional Collaboration Target Research and Development Plan (an ***"Amendment-Additional Collaboration Development Candidate"***) will be treated the same as an Oncology Development Candidate;

f. A finished product containing an Amendment-Additional Collaboration Target Compound as an active pharmaceutical ingredient (including any salt, hydrate, solvate or prodrug thereof) (a ***"Amendment-Additional Collaboration Target Product"***) will be treated the same as an Oncology Product;

And as such, except as explicitly set forth in this Amendment, each Party will have the same rights and obligations with respect to Amendment-Additional Collaboration Target Compounds and Amendment-Additional Collaboration Target Products as each has under

the Agreement with respect to Oncology Compounds and Oncology Products, including but not limited to:

a. the Option under Section 3.5 of the Agreement to obtain the license set forth in Section 6.1.3 of the Agreement;

b. and the applicable financial provisions under Article 8 of the Agreement as specified in Section 7 of this Amendment.

And the terms of the Agreement as they apply to the Amendment-Additional Collaboration Target, except where the context otherwise requires, shall be construed such that the Effective Date is replaced with the Amendment Date, including but not limited to Section 6.1.4 (e), 6.1.7, 6.2 of the Agreement and relevant definitions, including but not limited to "AstraZeneca Background IP"; and with respect to Section 3.2.2 of the Agreement where the Oncology Collaboration Term as it applies to the Amendment-Additional Collaboration Target will begin on the Amendment Date and will end on [***] (for the purposes of this Amendment herein referred to as the ***"Amendment-Additional Collaboration Term"***).

3. **No Substitution Rights.** The rights of substitution in Section 3.3.7 of the Agreement shall continue to apply to the Oncology Targets as set out therein but AstraZeneca will have no rights of substitution under the Agreement or this Amendment with respect to the Amendment-Additional Collaboration Target Program.

4. **Performing the Amendment-Additional Collaboration Target Research and Development Plan; Costs.**

a. Isis will use Commercially Reasonable Efforts to conduct the activities to be conducted by Isis designated under the Amendment-Additional Collaboration Target Research and Development Plan. Such activities will be treated the same as Isis Conducted Activities under the Agreement and the costs for such activities will be handled the same as the costs under Section 4.5.2 of the Agreement.

b. AstraZeneca will use Commercially Reasonable Efforts to conduct all other activities as described in the Amendment-Additional Collaboration Target Research and Development Plan. Such activities will be treated the same as AstraZeneca Conducted Activities under the Agreement and the costs for such activities will be handled the same as the costs under Section 4.5.2 of the Agreement.

5. **Manufacturing and Supply.**

The provisions of Section 4.6.1 (a) of the Agreement shall apply to Isis Conducted Activities designated under the Amendment-Additional Collaboration Target Research and Development Plan.

The provisions of Section 4.6.1 (b)(iii) (including the last two paragraphs of Section 4.6.1(b)) of the Agreement shall apply to AstraZeneca Conducted Activities under the

Amendment-Additional Collaboration Target Research and Development Plan, as more specifically set out herein:

a. ***Research Compound Supply***. Isis will provide up to [***] of bulk unformulated research-grade Compound for Amendment-Additional Collaboration Target Compounds for up to [***] for each of [***] ([***] total) [***]. In addition, should AstraZeneca require additional research-grade Compound for the Amendment-Additional Collaboration Target Program for pre-clinical studies, then, at AstraZeneca's reasonable request, Isis will use its reasonable endeavors to provide such research-grade Compound for such pre-clinical studies at [***].

b. ***Development API Supply***. Isis will supply (at AstraZeneca's expense at [***] within 60 days after AstraZeneca's receipt of the applicable invoice) bulk unformulated API for the Amendment-Additional Collaboration Development Candidate sufficient to support the IND Enabling Toxicology Studies for the Amendment-Additional Collaboration Target Development Candidate, and the quantity of API determined by the JSC when the protocol is available for the first Clinical Study, consistent with Isis' obligations to supply the Oncology Programs under Section 4.6.1(b)(iii) of the Agreement.

c. ***Formulation***. AstraZeneca will be responsible for conducting and paying for all formulation work to conduct the Amendment-Additional Collaboration Target Program. If requested by AstraZeneca, during the Amendment-Additional Collaboration Term Isis will provide reasonable assistance to AstraZeneca for such work as set out in the Amendment-Additional Collaboration Target Research and Development Plan. Isis will provide such assistance on an hourly basis [***] up to a reasonable maximum number of hours set by the Amendment-Additional Collaboration Target Working Group for each year of the Amendment-Additional Collaboration Term, and thereafter at Isis' then current FTE Rate. AstraZeneca will resupply any finished Product necessary to support any Isis Conducted Activities, AstraZeneca Conducted Activities, IND toxicology studies and the Phase 1 Study for the Amendment-Additional Collaboration Target Program.

d. ***Manufacturing Services Agreement.*** The Parties have entered into a Manufacturing Services Agreement with effective date of 7 March 2013 as provided by Section 4.6.1 (b) of the Agreement and the Parties agree that they will use the MSA to facilitate the supply arrangements herein.

6. **Amendment-Additional Collaboration Target Working Group**.

a. ***Formation of the Amendment-Additional Collaboration Target Working Group***. Within [***] ([***]) days after the Amendment Date, with respect to the Amendment-Additional Collaboration Target Program, the Parties will establish an Amendment-Additional Collaboration Target Working Group (***"Amendment-Additional Collaboration Target Working Group"***) that will be separate and

independent from the JSC, and will be responsible for the coordination and management of activities under the Amendment-Additional Collaboration Target Research and Development Plan. The Amendment-Additional Collaboration Target Working Group will consist of an equal number of representatives of each Party. The Amendment-Additional Collaboration Target Working Group will report into the JSC and will make decisions and resolve disputes in the same manner as the JSC.

b. ***Term of Amendment-Additional Collaboration Target Working Group***. The Amendment-Additional Collaboration Target Working Group (and any of its sub-teams and working groups) under this Amendment will cease to exist upon the earlier of Isis ceasing to participate in the JSC in respect of the Amendment-Additional Collaboration Target Program or the JSC ceasing to be responsible for making decisions in respect thereof, in each case as provided in Section 4.1.4 of the Agreement.

c. ***Meeting Coordination***. The Amendment-Additional Collaboration Target Working Group will meet at least once per quarter in person or via video conference or teleconference and more frequently whenever necessary and will meet in person at least twice a year. Isis and AstraZeneca will use commercially reasonable efforts to schedule meetings of the JSC and Amendment-Additional Collaboration Target Working Group to take place at the same location and on the same dates to maximize the use of each Party's time, increase information sharing efficiencies and reduce the cost of additional travel, lodging and related expenses.

7. **FTE hours.** Sections 6.5.1 and 7.1.5 of the Agreement will apply to the Amendment-Additional Collaboration Target in the same manner as applied to each Oncology Product, except the reference in those Sections to [***]. Instead, under each of Sections 6.5.1 and 7.1.5 of the Agreement up to [***] of Isis' time shall be available [***] to AstraZeneca (being [***] in total) specifically in respect of the Amendment-Additional Collaboration Target.

8. **Additional Financial Provisions.** The financial provisions set forth in Article 8 of the Agreement applicable to Oncology Products (including but not limited to Section 8.6 and Section 8.8) will apply to the Amendment-Additional Collaboration Target Products in the same manner as applied to each Oncology Product except that:

a. Section 8.1(iii) of the Agreement shall not apply with respect to the Amendment-Additional Collaboration Target Program, and instead Section 8.1 of the Agreement shall be amended to add that AstraZeneca shall pay Isis an additional up-front fee of $[***] in partial consideration for the Option granted by Isis to AstraZeneca under Section 3.5 for the Amendment-Additional Collaboration Target within 30 days after the Amendment Date;

b. In partial consideration for the Option granted by Isis to AstraZeneca under Section 3.5 of the Agreement in respect of the Amendment-Additional Collaboration Target, AstraZeneca will pay Isis $[***] when the Amendment-

Additional Collaboration Target Program achieves Target Sanction, such payment to be due within 30 days following receipt of an invoice from Isis following such achievement; and

c. Section 8.2 of the Agreement shall be amended such that up to a total of $[***] may become due and payable thereunder for a total of five Options (if AstraZeneca exercises all of its Options under the Agreement and under this Amendment and if a fourth Oncology Collaboration Program is added under Section 2.2.4 of the Agreement).

9. **Termination.** If the Amendment-Additional Collaboration Target Program has not achieved Target Sanction by [***], then either Party may terminate this Amendment by providing the other party a written notice thereof by [***] with the consequences thereof as set forth in Section 3.4 of the Agreement. The Amendment-Additional Collaboration Target Program (and therefore this Amendment) will terminate at the end of the Amendment-Additional Collaboration Term if, despite the Parties' Commercially Reasonable Efforts, by the expiration of the Amendment-Additional Collaboration term, Isis has not designated an Amendment-Additional Collaboration Target Lead Candidate, with the consequences thereof as set forth in Section 3.4 of the Agreement. The licenses under the Cross-Licensed Collaboration Formulation IP granted by each Party under Section 11.c of this Amendment will survive termination of this Amendment or the Agreement.

10. **Representations and Warranties**.

a. Each Party hereby makes, as of the Amendment Date and solely with respect to the Amendment-Additional Collaboration Target Program, the same representations and warranties set forth in Section 10.1 of the Agreement.

b. Isis hereby makes to AstraZeneca, as of the Amendment Date and solely with respect to the Amendment-Additional Collaboration Target Program, the same representations and warranties set forth in Section 10.2 of the Agreement.

11. **Intellectual Property Rights**.

a. Isis Patents. Solely with respect to the Amendment-Additional Collaboration Target Program, the Patent Rights listed on ATTACHMENT 2 to this Amendment (i) are part of the Isis Core Technology Patents and (ii) will not be considered formulation technology excluded under the definitions of Licensed Know-How or Licensed Patents, *except* that the Patent Rights listed on ATTACHMENT 2 to this Amendment (A) will be considered formulation technology for purposes of Section 8.9.3, 8.9.4 of the Agreement and the definition of Additional Core IP under the Agreement, and (B) [***]. The Patent Rights listed on ATTACHMENT 3 to this Amendment are part of the Isis Product-Specific Patents, solely with respect to the Amendment-Additional Collaboration Target Program.

b. [***] Agreements. It is agreed by AstraZeneca and Isis that the Amendment-Additional Collaboration Target Compounds will be treated as [***] under

AstraZeneca's agreements with [***] (the [***]), as such term is defined therein. As such, if clause (iv) of Section 3.4 of the Agreement or clause (i)(1) of Section 12.3.2 of the Agreement become applicable with respect to the Amendment-Additional Collaboration Target Program, then, subject to [***] right to use such results for research purposes as reserved to it in the [***], any results related to Amendment-Additional Collaboration Target Compounds owned by AstraZeneca under the [***] would be licensed to Isis under clause (iv) of Section 3.4 of the Agreement or clause (i)(1) of Section 12.3.2 of the Agreement, as the case may be. AstraZeneca will not provide [***] with any Amendment-Additional Collaboration Target Compounds unless and until [***] agrees in writing that such Compounds will be treated as [***] under the [***], and AstraZeneca will provide Isis such written agreement if requested by Isis. AstraZeneca will not amend (or waive any rights under) the [***] in any way that diminishes Isis' rights under this Section 11b without Isis' prior written consent.

c. Cross-Licenses to Collaboration Formulation IP. For purposes of this Amendment, ***"Cross-Licensed Collaboration Formulation IP"*** means (A) Patent Rights claiming formulation technology that is discovered, developed, invented, created or reduced to practice by or on behalf of a Party during the Agreement Term (i) in the performance of the Amendment-Additional Collaboration Target Plan, (ii) using the Amendment-Additional Collaboration Target Compounds, or (iii) using the inventions described in the Patent Rights listed on ATTACHMENT 2 to this Amendment, and (B) any Know-How related thereto, in each case to the extent Controlled by a Party at any time during the Agreement Term. Claims within a Patent Right claiming a specific combination of an Amendment-Additional Collaboration Target Compound and formulation technology will be Product-Specific Patents and will not be Cross-Licensed Collaboration Formulation IP. For purposes of the definition of Cross-Licensed Collaboration Formulation IP, [***].

i Isis hereby grants to AstraZeneca a perpetual, worldwide, non-exclusive, fully-paid, royalty-free, sublicensable license under the Cross-Licensed Collaboration Formulation IP to research, develop, manufacture, have manufactured, register, market and commercialize products.

ii AstraZeneca hereby grants to Isis a perpetual, worldwide, non-exclusive, sublicensable license under the Cross-Licensed Collaboration Formulation IP to research, develop, manufacture, have manufactured, register, market and commercialize products. *Notwithstanding the foregoing*, until the earlier of the [***] anniversary of the Amendment Date and the date Section 3.4 or Section 12.3.2 of the Agreement becomes applicable with respect to the Amendment-Additional Collaboration Target Program, Isis agrees that it will not (A) practice its license from AstraZeneca under any Patent Right within the Cross-Licensed Collaboration Formulation IP that is solely owned by AstraZeneca to develop, manufacture, have manufactured, register, market or commercialize products that [***] (such product, a ***"Restricted Product"***); *provided* that the restriction set forth in

this clause (A) will not preclude Isis from conducting research on any ASOs prior to designation of such ASOs as a development candidate; or (B) [***] a Restricted Product as [***] where such Restricted Product is Covered by a Patent Right within the Cross-Licensed Collaboration Formulation IP that is solely owned by AstraZeneca.

12. **No Impact on Other Collaboration Programs**. Except as otherwise expressly amended by this Amendment, the Agreement remains in full force and effect in accordance with its terms. For the avoidance of doubt, this Amendment is solely intended to modify certain terms of the Agreement regarding the Amendment-Additional Collaboration Target Program, and does not amend the Agreement in any way with respect to the [***] Program, [***] Program or any of the Oncology Collaboration Programs.

13. **Entire Agreement and Governing Law**. Section 14.9 of the Agreement shall be construed as including this Amendment. This Amendment shall be construed and interpreted as per the Agreement, including but not limited to governing law and jurisdiction, and defined terms set out in the Agreement shall have the same meaning in this Amendment unless otherwise provided by this Amendment.

* - * - * - *

[Signature page follows]

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

ISIS PHARMACEUTICALS, INC.

By: */s/ B. Lynne Parshall*

Name: B. Lynne Parshall

Title: _____

Date: _____

ASTRAZENECA AB

By: */s/ Jan-Olof Jacke*

Name: Jan-Olaf Jacke

Title: CFO, AstraZeneca AB

Date: 2013-08-13

ATTACHMENT 1

Amendment-Additional Collaboration Target Research and Development Plan

[***]

ATTACHMENT 2

Amendment-Additional Collaboration Target Isis Core Technology Patents

[***]

ATTACHMENT 3

Amendment-Additional Collaboration Target Isis Product Specific Patents

[***]

EXHIBIT 10.3

EXECUTION COPY

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

AMENDMENT NUMBER THREE
TO THE
AMENDED AND RESTATED
LICENSE AND COLLABORATION AGREEMENT

This Amendment Number Three (the "***Amendment***") to the Amended and Restated License and Collaboration Agreement is entered into as of the 2nd day of August, 2013 (the "***Effective Date***") by and among ALNYLAM PHARMACEUTICALS, INC., a Delaware corporation, with its principal place of business at 300 Third Street, Cambridge, Massachusetts 02142 ("***Alnylam***"), ISIS PHARMACEUTICALS, INC., a Delaware corporation, with its principal place of business at 2855 Gazelle Court, Carlsbad, California 92010 ("***Isis***", and each of Alnylam and Isis, a "***Licensor***" and together, the "***Licensors***"), and REGULUS THERAPEUTICS INC. (formerly Regulus Therapeutics LLC), a Delaware corporation, with its principal place of business at 3545 John Hopkins Court, San Diego, California 92121 ("***Regulus***").

RECITALS

WHEREAS, Isis and Alnylam each granted a license to Regulus in accordance with that certain License and Collaboration Agreement dated September 6, 2007 (the "***Original License Agreement***"), which Original License Agreement was amended and restated on January 1, 2009, and further amended on June 10, 2010 and October 25, 2011 (the "***Amended License Agreement***"); and

WHEREAS, Isis, Alnylam, and Regulus now desire to further amend the Amended License Agreement to, among other things, grant Regulus certain licenses and rights to the GalNac Process Technology, to the extent it relates to manufacturing; and to clarify Regulus' rights and restrictions on rights to transfer certain technology licensed to Regulus by Alnylam on the terms and conditions as provided below.

AGREEMENT

NOW, THEREFORE, in consideration of the mutual covenants contained herein, and other good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, Isis, Alnylam and Regulus each agrees as follows:

1. DEFINITIONS

Capitalized terms used herein and not defined elsewhere herein have the meanings set forth in the Amended License Agreement.

2. AMENDMENTS

2.1 Section 2.2(a) of the Amended License Agreement shall be deleted and replaced in its entirety by the following:

"(a) Grants. Subject to the terms and conditions of this Agreement (including but not limited to Section 2.4), each Licensor hereby grants to Regulus a worldwide, royalty-bearing, sublicenseable (in accordance with Section 2.5) license in the Field, under such Licensor's Licensed IP,

(i) to Develop miRNA Compounds and miRNA Therapeutics,

(ii) to Manufacture miRNA Compounds and miRNA Therapeutics, and

(iii) to Commercialize miRNA Therapeutics.

Subject to Section 2.4, the rights granted under clauses (i), (ii) and (iii) will be (x) exclusive with respect to miRNA Compounds which are miRNA Antagonists and miRNA Therapeutics containing such miRNA Compounds, (y) non-exclusive with respect to miRNA Compounds which are Approved Precursor Antagonists and miRNA Therapeutics containing such miRNA Compounds, and (z) non-exclusive with respect to Alnylam's Licensed IP that is GalNac ProcessTechnology."

2.2 Section 2.3(b) is hereby amended in its entirety as follows:

"(b) Regulus hereby grants to Isis a worldwide, exclusive, royalty-free, perpetual and irrevocable license, with the right to grant sublicenses, under the Regulus IP (*except* for Regulus IP (i) claiming the exact composition, i.e. specific sequence combined with chemistry, of a miRNA Mimic discovered by Regulus or (ii) that is an improvement to any GalNac Process Technology) solely to the extent necessary or useful to research, discover, develop, make, have made, use, sell, offer to sell and/or otherwise commercialize (i) single-stranded oligonucleotides or analogs thereof that are not miRNA Antagonists, Approved Precursor Antagonists, or Approved Mimics and (ii) any product containing single-stranded oligonucleotides or analogs thereof that are not miRNA Antagonists, Approved Precursor Antagonists, or Approved Mimics (the "*Isis Field*"); *provided* that in no event shall the rights granted above in any way restrict or otherwise prohibit Regulus from Researching, Developing, Manufacturing and Commercializing miRNA Mimics covered by such Regulus IP."

2.3 Section 2.5 is hereby amended by including the following Section 2.5(d) and 2.5(e):

"(d) Notwithstanding anything to the contrary in this Agreement, Regulus and its Affiliates may not transfer, sublicense, disclose or otherwise convey details of, any Alnylam Conjugate Technology, GalNac Process Technology, or Know-How or Patent Rights licensed to Regulus by Alnylam with respect to the delivery of oligonucleotides, to any Third Party, except that subject to Third Party Rights, Regulus and its Affiliates may:

(i) with the prior written consent of Alnylam, grant a sublicense of Regulus' rights to Alnylam Conjugate Technology and/or GalNac Process Technology under Section 2.2(a)(ii), to Third Party contract manufacturing organizations for the sole purpose of manufacturing a particular miRNA Therapeutic (or component thereof) on behalf of Regulus or its Affiliate;

(ii) upon written notice to Alnylam, grant a sublicense of Regulus' rights licensed under Section 2.2(a) to Alnylam Conjugate Technology, GalNac Process Technology, or Know-How or Patent Rights licensed to Regulus by Alnylam with respect to the delivery of oligonucleotides, to a Third Party with whom Regulus or its Affiliate has entered into a bona fide Development and Commercialization collaboration with respect to a particular Development Therapeutic; provided, that (x) such sublicense shall be limited to such Development Therapeutic, and (y) Alnylam's prior written consent shall be required if such Third Party or Third Party's Affiliate is in the business of providing contract manufacturing services;

(iii) with the prior written consent of Alnylam, grant a sublicense of Regulus' rights under Section 2.2(a)(ii) to Alnylam Conjugate Technology, GalNac Process Technology, or Know-How or Patent Rights licensed to Regulus by Alnylam with respect to the delivery of oligonucleotides, to a Third Party contract manufacturing organizations for the sole purpose of manufacturing a particular Development Therapeutic that is an Approved Mimic (or component of such Development Therapeutic) on behalf of Regulus or its Affiliate; and

(iv) upon written notice to Alnylam, grant a sublicense of Regulus' rights to Alnylam Conjugate Technology, GalNac Process Technology, or Know-How or Patent Rights licensed to Regulus by Alnylam with respect to the delivery of oligonucleotides, to a Third Party with whom Regulus or its Affiliate has entered into a bona fide Development and Commercialization collaboration with respect to a particular Development Therapeutic that is an Approved Mimic; provided, that (x) such sublicense shall be limited to such Development Therapeutic, and (y) Alnylam's prior written consent shall be required if such Third Party or Third Party's Affiliate is in the business of providing contract manufacturing services.

Alnylam's prior written consent shall be required for any further sublicenses by a Sublicensee of Regulus or its Affiliates described in this Section 2.5(d) to any Third Party in the business of providing contract manufacturing services. Alnylam's prior written consent under clause (i) and (iii) of this Section 2.5(d) may be withheld by Alnylam in its sole discretion, not to be unreasonably withheld.

(e) Regulus will and hereby does grant a sublicense of Regulus' rights to Alnylam Conjugate Technology and GalNac Process Technology under Section 2.2(a) to Isis in connection with Isis' exercise of its rights as an Opt-In Party; provided, that such sublicense shall be limited to the relevant Development Project's Development Compounds. The sublicensing restrictions in Section 2.5(d) shall also apply to Isis as an

Opt-In Party solely with respect to the sublicense by Isis of any GalNac Process Technology."

2.4 Section 3.1 is hereby deleted and replaced in its entirety by the following:

"3.1 Technology Transfer to Regulus. At each meeting of the Collaboration Working Group the representatives will discuss new Know-How and Patent Rights of Isis and Alnylam that are included in such Licensor's Licensed Patents and Licensed Know-How hereunder at the level of detail necessary to enable Regulus to effectively practice such Patent Rights and Know-How."

2.5 Section 9.2 of the Amended License Agreement is hereby amended by adding the following Section 9.2(c):

"(c) GalNac Process Technology. Notwithstanding anything in this Agreement to the contrary, (i) Alnylam has the sole right in its sole discretion, to file, prosecute, maintain, defend and enforce (including but not limited to, initiating a legal action against a Third Party with respect to the infringement of) any GalNac Process Technology Patent Rights, (ii) neither Regulus nor any Commercialization Party other than Alnylam shall have any rights under this Article 9 with respect to any Patent Rights or Know-How within the GalNac Process Technology, and (iii) Regulus will provide Alnylam, sufficiently in advance for Alnylam to comment, with copies of all patent applications and other material submissions and correspondence with, to or from any patent counsel or patent authorities pertaining to any Regulus IP that is an improvement to GalNac Process Technology, and Regulus will give due consideration to the comments of Alnylam, but will in good faith determine whether or not to incorporate such comments."

2.6 Exhibit 1 to the Amended License Agreement is hereby amended by adding the following Defined Terms:

"***Alnylam Conjugate Technology***" means Alnylam's Licensed IP that relates to GalNAc conjugate technology, other than GalNac Process Technology.

"***GalNac Process Technology***" means the (i) Know-How and (ii) Patent Rights, in each case that are Controlled by Alnylam as of the Effective Date, listed on Exhibit 3, which are comprised of manufacturing technology and other technology. No more than once per calendar year Regulus may request that this definition be expanded to include any improvements to such Know-How and Patent Rights listed on Exhibit 3. Alnylam agrees to consider such a request in good faith, but shall not be obligated to expand the definition of GalNac Process Technology to include such improvements."

2.7 Section 1.51 of Exhibit 1 of the Amended License Agreement shall be deleted and replaced in its entirety by the following:

"***Licensed Know-How***" means, with respect to a Licensor, all Know-How Controlled by such Licensor on the Effective Date or during the term of this Agreement (except as otherwise expressly provided herein) that relates to (a) miRNA Compounds or miRNA Therapeutics in general, (b) specific miRNA Compounds or miRNA Therapeutics, (c)

chemistry or delivery of miRNA Compounds or miRNA Therapeutics, (d) mechanism(s) of action by which a miRNA Antagonist directly prevents the production of a specific miRNA, or (e) methods of treating an Indication by modulating one or more miRNAs; provided, however, that in each case, (i) for any such Know-How that include financial or other obligations to a Third Party, the provisions of Section 2.4 will govern whether such Know-How will be included as Licensed Know-How and (ii) Licensed Know How does not include manufacturing technology (including but not limited to analytical methods), other than, in the case of Alnylam as Licensor, Know-How (to the extent related to manufacturing technology) included in the GalNac Process Technology."

2.8 Section 1.52 of Exhibit 1 of the Amended License Agreement shall be deleted and replaced in its entirety by the following:

"***Licensed Patent Rights***" means, with respect to a Licensor, (A) all Patent Rights Controlled by such Licensor on the Effective Date and listed on **Schedule 2.2(A)**, and (B) all Patent Rights Controlled by such Licensor during the term of this Agreement (except as otherwise expressly provided herein) that claim (a) miRNA Compounds or miRNA Therapeutics in general, (b) specific miRNA Compounds or miRNA Therapeutics, (c) chemistry or delivery of miRNA Compounds or miRNA Therapeutics, (d) mechanism(s) of action by which a miRNA Antagonist directly prevents the production of the specific miRNA, or (e) methods of treating an Indication by modulating one or more miRNAs; provided, however, that in each case, (i) for any such Patent Rights that include financial or other obligations to a Third Party, the provisions of Section 2.4 will govern whether such Patent Right will be included as a Licensed Patent Right and (ii) Licensed Patent Rights do not include manufacturing technology (including but not limited to analytical methods), other than, in the case of Alnylam as Licensor, Patent Rights (to the extent claiming manufacturing technology) included in the GalNac Process Technology."

2.9 The Amended License Agreement is hereby amended by including as Exhibit 3 to the Amended License Agreement, the Exhibit 3 (AlnylamGalNac Process Technology) attached hereto.

2.10 Concurrent with the Effective Date of this Amendment, and pursuant to Section 2.5(d)(i) above, Alnylam consents to a grant of a sublicense of Regulus' rights to Alnylam Conjugate Technology and Alnylam GalNac Process Technology under Section 2.2(a), [***] for the sole purpose of manufacturing its [***] miRNA Therapeutic (or component thereof) on behalf of Regulus or its Affiliate.

3. MISCELLANEOUS

3.1 **Other Terms**. All other terms and conditions of the Amended License Agreement shall remain in full force and effect.

3.2 **Counterparts**. This Agreement may be executed in any number of counterparts, each of which will be deemed all original, and all of which together will constitute one and the same instrument.

[Remainder of Page Intentionally Left Blank]

IN WITNESS WHEREOF, the Parties hereby execute this Amendment Number Three to the Amended and Restated License and Collaboration Agreement as of the date first written above.

ALNYLAM PHARMACEUTICALS, INC.

By: */s/ Lawrence Reid, Ph.D.*
Name: Lawrence Reid, Ph.D.
Title: Chief Business Officer

ISIS PHARMACEUTICALS, INC.

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

REGULUS THERAPEUTICS INC.

By: */s/ Kleanthis G. Xanthopoulos*
Name: Kleanthis G. Xanthopoulos, Ph.D.
Title: President and CEO

Exhibit 3

[***]

AMENDED AND RESTATED ISIS PHARMACEUTICALS, INC.
10B5-1 TRADING PLAN

This Amended and Restated 10b5-1 Trading Plan, (the "Trading Plan"), between **ISIS PHARMACEUTICALS, INC.** ("Isis") and **INSIGHT SECURITIES, INC.** ("Broker"), is entered into effective **September 12, 2013** (the "A&R Effective Date"). As of the Effective Date, this Trading Plan amends, restates and supersedes the previous 10b5-1 Trading Plan dated September 13, 2007 between Isis and Broker. Capitalized terms not otherwise defined herein will have the meanings given to them in Exhibit A attached hereto.

1. Recitals.

(a) This Trading Plan is entered into between Isis and Broker for the purpose of establishing a trading plan that complies with the requirements of Rule 10b5-1(c) under the Exchange Act.

(b) The purpose of this Trading Plan is to provide a mechanism by which eligible Sellers can orderly dispose of a portion of each Seller's holdings of Stock, including Stock that such Seller has the right to acquire under the Options.

(c) Isis and Broker hereby agree as follows:

2. Appointment. Isis hereby appoints and authorizes Broker to sell shares of Stock pursuant to the terms and conditions set forth below and in the applicable Sellers Plan. Subject to the terms and conditions set forth below, Broker hereby accepts such appointment.

3. Sellers Plans. Each Seller may establish up to three individual Sellers Plans with Broker in any Sales Period. For clarity, Sellers Plans pursuant to which all Plan shares have been sold will still count against the limit prohibiting more than three Sellers Plans in any Sales Period. In connection with such Sellers Plans, each Seller will establish an account at Broker in the name of and for the benefit of Seller (the "Plan Account"). Sales under each Sellers Plan cannot begin until the Broker receives (i) the Plan Shares (including any shares issued pursuant to restricted stock units), to the extent such Plan Shares are currently owned by Seller, (ii) a properly executed Seller Representation Letter and (iii) a properly completed and executed Sellers Plan, including an acknowledgment by Isis.

4. Obligations of Broker. With respect to each Sellers Plan, Broker will have the following obligations:

(a) Broker will sell the Plans Shares for the account of each Seller according to the terms of the Seller's Sellers Plan.

(b) Broker will not sell any Stock when broker is in possession of any material nonpublic information concerning Isis or its securities.

(c) Once a Sellers Plan becomes effective, Broker will not allow Seller to exercise, any influence over how, when or whether to effect sales of Stock pursuant to the Sellers Plan.

(d) Broker will withdraw Stock from Seller's Plan Account in order to effect sales of Stock under Seller's Sellers Plan. Broker will exercise Options in accordance with the instructions set forth in the applicable Sellers Plan.

(e) Broker will deliver the proceeds from each sale of unrestricted Stock effected under a Sellers Plan to Seller's Account on a normal three-day settlement basis less any commission, commission equivalent, mark-up or differential and other expenses of sale to be paid to Broker. With respect to each sale of restricted Stock, Broker will deliver the net proceeds from such sales as soon as reasonably practicable.

(f) Broker will, in connection with the exercise of Options, remit to Isis the exercise price thereof along with such amounts as may be necessary to satisfy withholding obligations. These amounts will be deducted from the proceeds of the sale of the Stock.

(g) To the extent that any Stock remains in the Plan Account upon termination of the Sellers Plan, Broker agrees to return such Stock promptly to the Seller.

(h) Broker agrees to conduct all sales pursuant to each Sales Plan in accordance with the manner of sale requirement of Rule 144 of the Securities Act and in no event will Broker effect any sale if such sale would exceed the then-applicable amount limitation under Rule 144 or will violate the "short-swing profit" provisions of Section 16 of the Exchange Act. Broker will file Forms 144 on behalf of Seller as required by applicable law.

(i) Promptly after each Sale, Broker will advise Seller in writing as to the number of shares of Stock sold, the date of each sale and the sales price. In addition, if a Seller is an officer of Isis who is subject to the reporting requirements of Section 16 under the Exchange Act, then Broker will provide Isis' stock administrator the details of each Trade for such Seller within 1 business day of such Trade, including the number of Plan Shares sold, the applicable sales price and any Options exercised to complete such Sale.

(j) Broker will suspend or terminate a Sellers Plan and cancel any pending sale upon notice from Isis of a Suspension Event (such notice to specify termination or suspension of the Sellers Plan). In the event of a suspension, Broker will cancel any open orders for sales of Plan Shares and will cease placing orders for Sales of Plan Shares under the Sellers Plan until Broker receives written notice from Isis stating that the relevant Suspension Event is no longer in effect. Upon Broker's receipt of notice from Isis, Broker may resume placing orders for sales of the Plan Shares in accordance with the terms and conditions of this Trading Plan and the applicable Sellers Plan; *provided*, *however*, that Broker will not reinstate any orders cancelled due to a suspension and will not place any orders that would have been placed during the suspension.

(k) Broker will not sell more than an aggregate of 50,000 shares on any single Trading Day for any individual Seller (including such Seller's trusts, spouse, or immediate family members) under all the Sellers Plans established by such Seller. Notwithstanding the

foregoing, Broker may sell more than this specified limit if (i) such sale is reasonably necessary to facilitate the exercise of Options that will expire within three Trading Days of such sale and (ii) the Company's Chief Operating Officer has authorized such a trade according to the notice provisions below.

(l) Unless a Seller's Sellers Plan explicitly instructs Broker to do otherwise, or Isis' COO or General Counsel approves otherwise, if Broker exercises an option because such Option was about to expire, Broker must sell the shares of Stock issued upon the exercise of such Option within 5 Trading Days of exercise at the then prevailing market price for the Stock, regardless of the Minimum Sales Prices set forth in the applicable Sellers Plan.

5. Termination; Amendment.

(a) Trading Plan. This Trading Plan may be Terminated by Isis at any time upon written notice to Broker. The parties hereto may amend this Trading Plan in writing by mutual written agreement.

(b) Voluntary Termination of Sellers Plan. Seller may terminate a Sellers Plan only during the last five Trading Days of a Sales Period by providing Broker and Isis advance written notice. The terminations will become effective at 5:00pm Pacific on the last day of the applicable Sales Period in which proper termination notice was given.

(c) Automatic Termination of Sellers Plan. An applicable Sellers Plan will automatically terminate on any of the following dates: (i) the date Broker is required to terminate the Sellers Plan under Section 4(j) of this Trading Plan, (ii) the 90th day following the date Broker receives notice of the death of the Seller or of Seller's termination from Isis, (iii) the date Isis or any other entity publicly announces a tender or exchange offer with respect to the Stock or a merger or acquisition of Isis, or (iv) the date Broker receives notice of the commencement or impending commencement of any proceeding relating to or triggered by Seller's bankruptcy or insolvency.

(d) Termination For Breach. Isis may terminate a Sellers Plan immediately upon the breach of a representation or covenant contained in the applicable Seller's Seller Representation Letter.

(e) No Amendment of Sellers Plan. Seller may not amend a Sellers Plan.

6. General.

(a) The prices and share amounts set forth in this Trading Plan and in each Sellers Plan will be automatically adjusted on a proportionate basis to take into account any stock split, stock dividend or any change in the capitalization similarly affecting Isis' Stock that occurs during the Sales Period.

(b) This Trading Plan, including exhibits, constitutes the entire agreement between the parties with respect to this Trading Plan and supercedes any prior agreements or understandings between the parties with regard to the Trading Plan.

(c) Any notice required to be given under this Trading Plan or a Sellers Plan will be addressed to the relevant party at the address set forth below.

To Broker:
InSight Securities, Inc.
2511 Garden Road, Suite C-225
Monterey, CA 93940
Attn: Peter Albano
Fax: (831) 648-1951
Phone: (866) 648-8010

w/copy to:
InSight Securities, Inc.
Attn: Carlos J. Legaspy
2610 Lake Cook Road, Suite 190
Riverwoods, IL 60015
Fax: (224) 632-4592
Phone: (224) 632-4700

To Isis:
Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attn: Chief Operating Officer
Fax: 760-268-4922
Phone: 760-603-2460

with copies to:
Linda Powell
Fax: 760-918-3593

To Seller:
The contact information specified in the applicable Seller Representation Letter.

Notice will be deemed sufficiently given for all purposes upon the earlier of: (a) the date of actual receipt; (b) if mailed, three (3) calendar days after the date of postmark; (c) if delivered by overnight courier, the next business day such overnight courier regularly makes deliveries; or (d) if sent by facsimile,

when the sender's facsimile system generates a message confirming successful transmission of the total number of pages of the notice unless, within one business day after the transmission, the recipient informs the sender that the recipient has not received the entire notice.

(d) This Trading Plan may be signed in counterparts, each of which will be an original, with the same effect as if the signatures thereto and hereto were upon the same instrument.

(e) If any provision of this Trading Plan is or becomes inconsistent with any applicable present or future law, rule or regulation, that provision will be deemed modified or, if

necessary, rescinded in order to comply with the relevant law, rule or regulation. All other provisions of this Trading Plan will continue and remain in full force and effect.

(f) This Trading Plan and any Sellers Plan is not an employment contract and nothing in such plans will create in any way whatsoever any obligation on a Seller's part to continue in the employ of Isis, or of Isis to continue Seller's employment with Isis.

(g) In the event of any conflict between the provisions of a Sellers Plan and those of this Trading Plan, the provisions of this Trading Plan will control. Isis' General Counsel has the power to construe and interpret this Trading Plan and any Sellers Plan, and to establish, amend and revoke rules for its administration. Isis' General Counsel in the exercise of this power may correct any defect, omission or inconsistency in this Trading Plan or any Sellers Plan.

(h) The parties' rights and obligations under this Trading Plan will bind and inure to the benefit of their respective successors, heirs, executors, and administrators and permitted assigns.

IN WITNESS WHEREOF, the undersigned have entered into this Trading Plan as of the date first written above.

ISIS PHARMACEUTICALS, INC.

/s/ B. Lynne Parshall
B. Lynne Parshall
Chief Operating Officer

INSIGHT SECURITIES, INC.

/s/ Carlos J. Legaspy
Carlos J. Legaspy
President

EXHIBIT A
DEFINITIONS

"Daily Sales Amount" has the meaning set forth in the applicable Sellers Plan.

"Effective Date" means, with respect to a Sellers Plan, the date the Seller Representation Letter was executed by Seller and accepted by Broker.

"Exchange Act" means the Securities Exchange Act of 1934, as amended.

"Options" means the outstanding stock options issued by Isis listed in the applicable Sellers Plan.

"Minimum Sales Price" has the meaning set forth in the applicable Sellers Plan.

"Plan Shares" means (i) the Stock and (ii) the Stock issuable upon exercise of the Options, to be sold pursuant to the Sellers Plan.

"Rule 144" means Rule 144 under the Securities Act.

"Sales Period" The Sales Period at the time of the A&R Effective Date began on October 1, 2012 and will end on September 30, 2013. The next Sales Period will begin on October 1, 2013 and will end on June 30, 2014. Thereafter, Sales Periods will begin every year on July 1 (beginning with July 1, 2014) and will end on June 30 of the following year until this Trading Plan or the applicable Sellers Plan is terminated.

"Sellers Plan" means a Sellers Plan in the form attached hereto as Exhibit B entered into between Broker and a Seller.

"Securities Act" means the Securities Act of 1933, as amended.

"Seller Representation Letter" is the seller representation letter, a form of which is attached hereto as Exhibit C.

"Seller" means Isis' executive officers, members of its Board of Directors and other individuals specified by Isis who participate in the Trading Plan and who have agreed to only sell Stock under the Trading Plan.

"Stock" means the common stock, $0.001 par value per share, of Isis.

"Suspension Event" means a legal, contractual or regulatory restriction that is applicable to Seller or Seller's affiliates that does not permit the execution of sales made under a Sellers Plan (other than any such restriction relating to Seller's possession or alleged possession of material nonpublic information about Isis or its securities subsequent to the execution of the Sellers Plan), including, without limitation, (i) any restriction related to a merger or acquisition, (ii) a stock offering requiring an affiliate lock-up, that would prohibit any sale pursuant to the Trading Plan, or (iii) a potential violation of Section 16 of the Exchange Act.

"Trading Day" means any day during the Sales Period that (i) the Nasdaq Stock Market is open for business and the Stock trades regularly on such day and (ii) Isis is open for business as a corporation.

EXHIBIT B
SELLERS PLAN

Seller's Name:
Seller's Account Number:
Effective Date: **;** *provided however*, that Broker will not make any trades under this Sellers Plan until the start of the general trading session on the 30th calendar day following the Effective Date (i.e.).

Plan Shares:

shares of Stock owned by Seller; and/or

shares of Stock issuable upon the exercise of the Options listed on the table below (*vested shares only*).

Instructions:

For the shares of Stock owned by Seller the Sales Amount and Minimum Sales Price will be as follows:

Sales Amount	Minimum Sales Price	If Stock received under ESPP Plan or from an RSU, please indicate original issue date and original issue price for Stock and "RSU" or "ESPP" as applicable

For the shares of Stock issuable upon the exercise of the Options the Sales Amount and Minimum Sales Price will be as follows.

Option Number	Sales Amount	Exercise Price	Expiration Date	Minimum Sales Price

During the Sales Period, Broker will sell the number of shares of Stock identified in each row of the tables above (the "Sales Amount") for the account of Seller on each Trading Day under ordinary principles of best execution at the then-prevailing market price; provided that Broker will not sell any shares of Stock under a Sellers Plan at a price of less than the Minimum Sales Price.

If, consistent with ordinary principles of best execution, Broker cannot sell the Sales Amount on any Trading Day, then the amount of such shortfall may be sold as soon as practicable on the immediately succeeding Trading Day and on each subsequent Trading Day as is necessary to sell such shortfall consistent with the ordinary principals of best execution. If any shortfall exists after the close of trading on the last Trading Day prior to the termination of this Trading Plan or the applicable Sellers Plan, Broker's obligation and authorization to sell such shares will terminate.

If the Minimum Sales Price for two different blocks of Plan Shares is reached in the same Trading Day, Broker will attempt to sell the Plan Shares allocated to the higher Minimum Sales Price first.

Uptrend Discretion

o On any Trading Day in which the Minimum Sales Price is reached, if the Broker reasonably and in good faith believes there is an upward trend in the trading price of Isis' stock, then Broker may in its discretion choose not to sell the Sales Amount at the Minimum Sales Price on such Trading Day with the prospect of later selling the Sales Amount at a price that is higher than the then current market price. So long as Broker exercises its discretion under this provision in good faith, Broker will have no liability to Seller for failing to sell any Plan Shares on a Trading Day in which the Minimum Sales Price for such Plan Shares was achieved.

No Expiration of In-the-Money Options:

In the event that unexercised Options are about to expire or terminate, Broker will exercise such Options at its discretion during the last:

(Please Check Only One of the Following)

o 5 Trading Days prior to the expiration/termination date of the Options

o 30 Trading Days prior to the expiration/termination date of the Options

o 60 Trading Days prior to the expiration/termination date of the Options

o Trading Days prior to the expiration/termination date of the Options

Broker will in no event exercise any Option if at the time of exercise the exercise price of the Option is equal to or higher than then current market price of the Stock.

ESPP Shares

o If Seller purchases shares through the Isis Employee Stock Purchase Plan at any time during the Sales Period, the newly purchased shares will automatically become part of this Sellers Plan as Plan Shares and Broker will sell such shares according to the following instructions:

RSU Shares

o If Seller receives shares through from Restricted Stock Units under the Isis 2011 Equity Incentive Plan at any time during the Sales Period, the newly received shares will automatically become part of this Sellers Plan as Plan Shares and, once Broker confirms receipt of such shares, Broker will sell such shares according to the following instructions:

Other Instructions:

EXHIBIT C

SELLER REPRESENTATION LETTER

Seller Representation and Covenant Letter

Date:

Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010

InSight Securities, Inc.
2511 Garden Road, Suite C-225
Monterey, CA 93940
Attn: Peter Albano

In connection with the Seller's Sellers Plan under the 10b5-1 Trading Plan (the "Trading Plan") of Isis Pharmaceuticals, Inc. ("Isis"), the Seller makes the representations and agrees to the covenants set forth below.

All capitalized terms that are not otherwise defined herein shall have the meanings ascribed to them in the Trading Plan. The terms of the Trading Plan are incorporated herein by reference. In the event of any conflict between the provisions of this letter and the Trading Plan, the provisions of the Trading Plan will control.

Seller hereby appoints and authorizes Broker to sell shares of Stock pursuant to the terms and conditions of the Trading Plan and the Sellers Plan attached hereto and incorporated herein by reference as Exhibit I (the "Sellers Plan"). Broker hereby accepts such appointment.

Seller Representations.

1. Sales of Stock under the Sellers Plan have been approved by an authorized representative of Isis.

2. As of the date hereof, Seller is not aware of any material nonpublic information concerning Isis or its securities. Seller is entering into the Sellers Plan in good faith and not as part of a plan or scheme to evade compliance with the federal securities laws.

3. The Stock to be sold under the Sellers Plan is owned free and clear by Seller (subject, in the case of shares underlying Options, only to the compliance by Seller with the exercise provisions of such options) and is not subject to any agreement granting any pledge, lien, mortgage, hypothecation, security interest, charge, option or encumbrance or any other limitation on disposition, other than those which may have been entered into between Seller and Broker or imposed by Rules 144 or 145 under the Securities Act.

4. Seller has had an opportunity to discuss the Sellers Plan with his or her own advisors as to the legal, tax, business, financial and related aspects of the Sellers Plan and has determined that the Sellers Plan meets the affirmative defense criteria set forth in Rule 10b5-

1(c). Seller has not relied upon Broker or Isis (or any person affiliated with Broker or Isis) in connection with, Seller's adoption and implementation of the Sellers Plan.

5. Seller acknowledges and agrees that, once the Sellers Plan becomes effective, Seller does not have, and shall not attempt to exercise, any influence over how, when or whether to effect sales of Stock pursuant to the Sellers Plan.

Seller Covenants.

6. While the Sellers Plan is in effect, Seller agrees not to (i) buy or sell any securities of Isis outside of the transactions contemplated by the Trading Plan and purchases pursuant to Isis' Employee Stock Purchase Plan, (ii) enter into or alter any corresponding or hedging transaction or position with respect to the Stock covered by the Sellers Plan (including, without limitation, with respect to any securities convertible or exchangeable into the Stock), and (iii) alter or deviate from the terms of the Sellers Plan.

7. Seller agrees to deliver to Broker the Plan Shares (including any shares issued pursuant to restricted stock units) pursuant to the Sellers Plan to be placed into Seller's Plan Account prior to the commencement of sales under the Sellers Plan.

8. Seller agrees that, with respect to shares of Stock issuable upon the exercise of Options, Seller may only include shares that are vested as of the 30th day following the Effective Date of the applicable Sellers Plan.

9. Seller agrees to make appropriate arrangements with Isis and its transfer agent and stock plan administrator to permit Broker to furnish notice to Isis of the exercise of the Options and to have underlying shares delivered to Broker as necessary to effect sales under the Sellers Plan. Seller hereby authorizes and appoints each of Broker and Isis' Chief Operating Officer to serve, individually or collectively, as Seller's agent and attorney-in-fact and, in accordance with the terms of the Sellers Plan, to exercise the Options. Seller agrees to complete, execute and deliver to Broker cashless exercise forms, in sufficient form to allow for the exercise of Options pursuant to the Sellers Plan at such times and in such numbers as Broker may reasonably request.

10. Seller will not, directly or indirectly, communicate any information relating to the Stock or Isis to any employee of Broker or its affiliates who is involved, directly or indirectly, in executing the Sellers Plan at any time while the Sellers Plan is in effect.

11. Seller agrees to notify Broker's compliance office by telephone or facsimile as soon as practicable if Seller becomes aware of the occurrence of any Suspension Event. Such notice will indicate the anticipated duration of the restriction, but will not include any other information about the nature of the restriction or its applicability to Seller and will not in any way communicate any material nonpublic information about Isis or its securities to Broker.

12. Seller understands and agrees that so long as it is an "affiliate" of Isis for purposes of Rule 144 under the Securities Act, all sales under the Plan will be in accordance with Rule 144. Seller agrees not to take any action that would cause Seller to aggregate sales under the Sellers Plan with sales of other securities of the issuer pursuant to Rule 144, and not to take any action that would cause the sales under the Plan not to comply with Rule 144.

13. Seller agrees to complete, execute and deliver to Broker Forms 144 for the sales to be effected under the Sellers Plan at such times and in such numbers as Broker reasonably requests. The "Remarks" section of each Form 144 will state that the sale is being made pursuant to a previously adopted plan intended to comply with Rule 10b5-1(c) and will indicate the date the Sellers Plan was adopted and that the representation is made as of such date.

14. Seller agrees to make all filings, if any, required under Sections 13(d), 13(g) and 16 of the Exchange Act in a timely manner, to the extent any such filings are applicable to Seller.

15. Seller agrees that Seller will at all times during the Sales Period, in connection with the performance of the Sellers Plan, comply with all applicable laws, including, without limitation, Section 16 of the Exchange Act and the rules and regulations promulgated thereunder.

16. Seller will notify Broker and Isis of any other purchase or sale transactions involving securities of Isis that are not contemplated by the Trading Plan.

17. If Seller wishes to transfer any Plan Shares (i) Seller must comply with Isis' policies regarding the transfer of such Plan Shares, and (ii) the transferee must agree to assume and be bound by the terms of the applicable Sellers Plan and execute a representation and covenant letter substantially in the form of this representation and covenant letter.

Very truly yours,

_____

[name]
[address]
[telephone]
[fax]

Agreed:

InSight Securities, Inc.

Accepted:

Isis Pharmaceuticals, Inc.

By: _____

Its: _____

B. Lynne Parshall
Chief Operating Officer

EXHIBIT 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Isis Pharmaceuticals, Inc.;

2. Based on my knowledge, this quarterly report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this quarterly report;

3. Based on my knowledge, the condensed consolidated financial statements, and other financial information included in this quarterly report, fairly present in all material respects the financial condition, condensed consolidated results of operations and condensed consolidated cash flows of the registrant as of, and for, the periods presented in this quarterly report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: November 5, 2013

/s/ Stanley T. Crooke

Stanley T. Crooke, M.D., Ph.D.
Chief Executive Officer

EXHIBIT 31.2

CERTIFICATION

I, Elizabeth L. Hougen, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Isis Pharmaceuticals, Inc.;

2. Based on my knowledge, this quarterly report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this quarterly report;

3. Based on my knowledge, the condensed consolidated financial statements, and other financial information included in this quarterly report, fairly present in all material respects the financial condition, condensed consolidated results of operations and condensed consolidated cash flows of the registrant as of, and for, the periods presented in this quarterly report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: November 5, 2013

/s/ Elizabeth L. Hougen

Elizabeth L. Hougen
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 Elizabeth L. Hougen, the Chief Financial Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

1. The Company's Quarterly Report on Form 10-Q for the period ended September 30, 2013, to which this Certification is attached as Exhibit 32.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

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

Dated: November 5, 2013

/s/ Stanley T. Crooke	/s/ Elizabeth L. Hougen
Stanley T. Crooke, M.D., Ph.D.	Elizabeth L. Hougen
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.