UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

Form 10-Q

(Mark One)

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

For the Quarterly Period Ended September 30, 2015

OR

☐ 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 ☒ No ☐

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 ☒ No ☐

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 ☒	Accelerated filer ☐
Non-accelerated filer ☐ (Do not check if a smaller reporting company)	Smaller reporting company ☐

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 ☐ No ☒

The number of shares of voting common stock outstanding as of November 4, 2015 was 120,117,708.

ISIS PHARMACEUTICALS, INC.
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TRADEMARKS

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

Akcea Therapeutics™ is a trademark of Isis Pharmaceuticals, Inc.

Regulus Therapeutics™ is a trademark of Regulus Therapeutics Inc.

KYNAMRO® is a registered trademark of Genzyme Corporation

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

	September 30, 2015 (Unaudited)	December 31, 2014
ASSETS		
Current assets:		
Cash and cash equivalents	$ 126,593	$ 142,998
Short-term investments	685,599	585,834
Contracts receivable	1,826	3,903
Inventories	6,583	6,290
Investment in Regulus Therapeutics Inc.	18,594	81,881
Other current assets	29,066	15,691
Total current assets	868,261	836,597
Property, plant and equipment, net	89,243	88,958
Licenses, net	1,285	2,690
Patents, net	19,489	17,186
Deposits and other assets	9,727	10,378
Total assets	$ 988,005	$ 955,809
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 19,294	$ 17,984
Accrued compensation	9,508	12,302
Accrued liabilities	24,487	30,451
Current portion of long-term obligations	773	2,882
Current portion of deferred contract revenue	68,136	51,713
Total current liabilities	122,198	115,332
Long-term deferred contract revenue	149,100	127,797
1 percent convertible senior notes	342,136	327,486
2¾ percent convertible senior notes	49,754	48,014
Long-term obligations, less current portion	7,312	7,669
Long-term financing liability for leased facility	72,091	71,731
Total liabilities	742,591	698,029
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 120,028,312 and 118,442,726 shares issued and outstanding at September 30, 2015 and December 31, 2014, respectively	120	118
Additional paid-in capital	1,286,690	1,224,509
Accumulated other comprehensive (loss) income	(17,957)	39,747
Accumulated deficit	(1,023,439)	(1,006,594)
Total stockholders' equity	245,414	257,780
Total liabilities and stockholders' equity	$ 988,005	$ 955,809

See accompanying notes.

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,	
	2015	**2014**	**2015**	**2014**
Revenue:				
Research and development revenue under collaborative agreements	$ 48,918	$ 43,798	$ 230,469	$ 119,975
Licensing and royalty revenue	203	265	1,664	9,325
Total revenue	49,121	44,063	232,133	129,300
Expenses:				
Research, development and patent expenses	88,508	61,086	220,962	173,798
General and administrative	8,751	4,470	23,992	13,313
Total operating expenses	97,259	65,556	244,954	187,111
Loss from operations	(48,138)	(21,493)	(12,821)	(57,811)
Other income (expense):				
Investment income	1,185	675	2,946	2,003
Interest expense	(9,233)	(4,998)	(27,381)	(14,902)
Gain on investments, net	199	3	200	140
Gain on investment in Regulus Therapeutics Inc.	20,211	535	20,211	535
Loss before income tax expense	(35,776)	(25,278)	(16,845)	(70,035)
Income tax expense	—	(1,398)	—	(2)
Net loss	$ (35,776)	$ (26,676)	$ (16,845)	$ (70,037)
Basic and diluted net loss per share	$ (0.30)	$ (0.23)	$ (0.14)	$ (0.60)
Shares used in computing basic and diluted net loss per share	119,979	117,811	119,560	117,511

See accompanying notes.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2015	2014	2015	2014
Net loss	$ (35,776)	$ (26,676)	$ (16,845)	$ (70,037)
Unrealized losses on securities, net of tax	(16,157)	(6,994)	(37,493)	(3,189)
Reclassification adjustment for realized gains included in net loss	(20,211)	(831)	(20,211)	(997)
Comprehensive loss	$ (72,144)	$ (34,501)	$ (74,549)	$ (74,223)

See accompanying notes.

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

	Nine Months Ended September 30,	
	2015	**2014**
Operating activities:		
Net loss	$ (16,845)	$ (70,037)
Adjustments to reconcile net loss to net cash provided by (used in) operating activities:		
Depreciation	5,190	4,791
Amortization of patents	1,012	841
Amortization of licenses	1,405	1,412
Amortization of premium on investments, net	5,495	5,649
Amortization of debt issuance costs	841	412
Amortization of 2¾ percent convertible senior notes discount	1,741	5,103
Amortization of 1 percent convertible senior notes discount	14,651	—
Amortization of long-term financing liability for leased facility	4,994	4,962
Stock-based compensation expense	41,907	22,894
Gain on investment in Regulus Therapeutics Inc.	(20,211)	(535)
Gain on investments, net	(200)	(140)
Non-cash losses related to patents, licensing and property, plant and equipment	244	753
Tax benefit from other unrealized gains on securities	—	—
Changes in operating assets and liabilities:		
Contracts receivable	2,077	(15,211)
Inventories	(293)	948
Other current and long-term assets	(13,257)	(1,239)
Accounts payable	862	1,414
Accrued compensation	(2,794)	(5,004)
Deferred rent	163	126
Accrued liabilities	(6,109)	7,046
Deferred contract revenue	37,726	(28,584)
Net cash provided by (used in) operating activities	58,599	(64,399)
Investing activities:		
Purchases of short-term investments	(398,076)	(250,580)
Proceeds from the sale of short-term investments	293,109	222,896
Purchases of property, plant and equipment	(5,281)	(3,969)
Acquisition of licenses and other assets, net	(3,334)	(2,443)
Proceeds from the sale of Regulus	25,527	—
Proceeds from the sale of strategic investments	39	2,036
Net cash used in investing activities	(88,016)	(32,060)
Financing activities:		
Proceeds from equity awards	20,275	17,709
Principal payments on debt and capital lease obligations	(7,263)	(8,003)
Net cash provided by financing activities	13,012	9,706
Net decrease in cash and cash equivalents	(16,405)	(86,753)
Cash and cash equivalents at beginning of period	142,998	159,973
Cash and cash equivalents at end of period	$ 126,593	$ 73,220
Supplemental disclosures of cash flow information:		
Interest paid	$ 4,233	$ 2,977
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 447	$ 3,204

See accompanying notes.

1. Basis of Presentation

The unaudited interim condensed consolidated financial statements for the three and nine months ended September 30, 2015 and 2014 have been prepared on the same basis as the audited financial statements for the year ended December 31, 2014. 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, 2014 included in our Annual Report on Form 10-K filed with the Securities and Exchange Commission, or SEC.

The condensed consolidated financial statements include the accounts of Isis Pharmaceuticals, Inc. ("we", "us" or "our") and our wholly owned subsidiary, Akcea Therapeutics, Inc., which we formed in December 2014.

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 the instances in which we have received payment from our customers in advance of recognizing revenue, we include the amounts in deferred revenue on our consolidated condensed balance sheet.

Arrangements with multiple deliverables

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, and we allocate the consideration to each unit of accounting based on the relative selling price of each deliverable.

Identifying deliverables and units of accounting

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. For example, in May 2015, we entered into an exclusive license agreement with Bayer to develop and commercialize ISIS-FXI$_{Rx}$ for the prevention of thrombosis. As part of the agreement, Bayer paid us a $100 million upfront payment in the second quarter of 2015. We are also eligible to receive milestone payments, license fees and tiered royalties on gross margins of ISIS-FXI$_{Rx}$. We are responsible for completing the ongoing development services for ISIS-FXI$_{Rx}$ and for providing an initial supply of active pharmaceutical ingredient, or API. Bayer is responsible for all other development and commercialization activities for ISIS-FXI$_{Rx}$. Since this agreement has multiple elements, we evaluated the deliverables in this arrangement when we entered into the agreement and determined that certain deliverables have stand-alone value. Below is a list of the three units of accounting under our agreement:

- The exclusive license we granted to Bayer to develop and commercialize ISIS-FXI$_{Rx}$ for the treatment of thrombosis;
- The development services we agreed to perform for ISIS-FXI$_{Rx}$; and
- The initial supply of API.

We determined that each of these three units of accounting have stand-alone value. The exclusive license we granted to Bayer has stand-alone value because it is an exclusive license that gives Bayer the right to develop ISIS-FXI$_{Rx}$ or to sublicense its rights. The development services and the initial supply of API have stand-alone value because Bayer or another third party could provide these items without our assistance.

Measurement and allocation of arrangement consideration

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 initially allocate the amount of consideration that is fixed and determinable at the time the agreement is entered into and exclude contingent consideration. 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 stand-alone 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.

We determined that the allocable arrangement consideration for the Bayer collaboration was $100 million and we allocated it based on the relative BESP of each unit of accounting. We engaged a third party, independent valuation expert to assist us with determining BESP. We estimated the selling price of the license granted for ISIS-FXI$_{Rx}$ by using the relief from royalty method. Under this method, we estimated the amount of income, net of taxes, for ISIS-FXI$_{Rx}$. We then discounted the projected income to present value. The significant inputs we used to determine the projected income of the license 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 ongoing development services by using our internal estimates of the cost to perform the specific services and estimates of expected cash outflows to third parties for services and supplies over the expected period that we will perform the development services. The significant inputs we used to determine the selling price of the ongoing development services included:

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

We determine the selling price of our API consistently for all of our partnerships. On an annual basis, we calculate our fully absorbed cost to manufacture API. We then determine the unit price we will charge our partners by dividing our fully absorbed costs by the quantity of API we expect to produce during the year.

For purposes of determining the BESP of the services we will perform and the API in our Bayer transaction, we were required to include a markup for a reasonable profit margin.

Based on the units of accounting under the agreement, we allocated the $100 million upfront payment from Bayer as follows:

- $91.2 million to the ISIS-FXI$_{Rx}$ exclusive license;
- $4.3 million for ongoing development services; and
- $4.5 million for the delivery of API.

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-FXI$_{Rx}$ license, we determined that the revenue we would have allocated to the ISIS-FXI$_{Rx}$ license would change by approximately one percent, or $0.9 million, from the amount we recorded.

Timing of revenue recognition

We recognize revenue as we deliver each item under the arrangement and the related revenue is realizable and earned. For example, we recognized revenue for the exclusive license we granted Bayer for ISIS-FXI$_{Rx}$ in the second quarter of 2015 because that was when we delivered the license. We also recognize revenue over time. Our collaborative agreements typically include a research and/or development project plan outlining the activities the agreement requires each party to perform during the collaboration. We must estimate our period of performance when the agreements we enter into do not clearly define such information. 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. We then recognize revenue ratably over such period. We have made estimates of our continuing obligations under numerous agreements and in certain instances the timing of satisfying these obligations may change as the development plans for our drugs progress. Accordingly, our estimates may change in the future. If our estimates and judgments change over the course of our collaboration agreements, it may affect the timing and amount of revenue that we recognize in future periods.

The following are the periods over which we are recognizing revenue for each of our units of accounting under our Bayer agreement:

- We recognized the portion of the consideration attributed to the ISIS-FXI$_{Rx}$ license immediately because we delivered the license and earned the revenue;
- We are recognizing the amount attributed to the ongoing development services for ISIS-FXI$_{Rx}$ over the period of time we are performing the services; and
- We will recognize the amount attributed to the API supply when we deliver it to Bayer.

Multiple agreements

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:

- In January 2012, we entered into a collaboration agreement with Biogen to develop and commercialize nusinersen (formerly 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 nusinersen through completion of Phase 2/3 clinical trials.

- In June 2012, we entered into a second and separate collaboration agreement with Biogen 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 to discover and develop antisense drugs against three targets to treat neurological or neuromuscular disorders. As part of the collaboration, we received $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 to leverage antisense technology to advance the treatment of neurological diseases. We granted Biogen 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 identified during the six year term of this collaboration, while Biogen is responsible for the creation and development of small molecule treatments and biologics.

All four of these collaboration agreements give Biogen the option to license one or more drugs resulting from the specific collaboration. If Biogen 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 achieves pre-specified regulatory milestones, and royalties on any product sales of drugs resulting from these collaborations.

We evaluated all four of the Biogen 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 deliverables, 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 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 estimated period of our performance.

Milestone payments

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

Prior to the first stage in the life-cycle of our drugs, we perform a significant amount of work using our proprietary antisense technology to design chemical compounds 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 partnered 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 us or 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 immediately. 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 access to new technologies we discover, we have determined that the majority of future development, regulatory and commercialization milestones are substantive. For example, we consider most of the milestones associated with our strategic alliance with Biogen substantive because we are using our antisense drug discovery platform to discover and develop new drugs against targets for neurological diseases. We also consider milestones associated with our strategic alliance with Alnylam Pharmaceuticals, Inc. substantive because we provide Alnylam ongoing access to our technology to develop and commercialize RNA interference, or RNAi, therapeutics. 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 in 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 our estimated period of performance, if any. Further information about our collaborative arrangements can be found in Note 6, *Collaborative Arrangements and Licensing Agreements*.

Licensing and royalty revenue

We often enter into agreements to license our proprietary patent rights on an exclusive or non-exclusive basis in exchange for license fees and/or royalties. We generally recognize as revenue immediately those licensing fees and royalties for which we have no significant future performance obligations and are reasonably assured of collecting the resulting receivable. For example, in the first quarter of 2014, we recognized $7.7 million in revenue from Alnylam related to its license of our technology to one of its partners because we had no performance obligations and collectability was reasonably assured.

Cash, cash equivalents and short-term investments

We consider all liquid investments with maturities of three months or less when we purchase them to be cash equivalents. Our short-term investments have initial maturities of greater than three months 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, 2015, we held ownership interests of less than 20 percent in each of the respective companies.

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. We hold one cost method investment in Atlantic Pharmaceuticals Limited. Realization of our equity position in this company is uncertain. When realization of our investment is uncertain, 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, or FIFO. 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 nine months ended September 30, 2015 and 2014. Total inventory, which consisted of raw materials, was $6.6 million and $6.3 million as of September 30, 2015 and December 31, 2014, respectively.

Research, development and patent expenses

Our research and development expenses 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. We expense research and development costs as we incur them. When we make payments for research and development services prior to the services being rendered, we record those amounts as prepaid assets on our condensed consolidated balance sheet and we expense them as the services are provided.

We capitalize costs consisting principally of outside legal costs and filing fees related to obtaining patents. We amortize patent costs over the useful life of the patent, beginning with the date the United States Patent and Trademark Office, or foreign equivalent, issues the patent. 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.

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.

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, 2015 and 2014, 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. Common stock from the following would have had an anti-dilutive effect on net loss per share:

- 1 percent convertible senior notes;
- 2¾ percent convertible senior notes;
- Dilutive stock options;
- Unvested restricted stock units; and
- Employee Stock Purchase Plan, or ESPP.

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, 2015 and December 31, 2014, we had collaborative arrangements with two entities, Regulus and Antisense Therapeutics Limited, that we considered to be variable interest entities. We are not the primary beneficiary for any of these entities as we do not have the power to direct the activities that most significantly impact the economic performance of our variable interest entities, 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, 2015, the total carrying value of our investments in variable interest entities was $18.6 million, and was related to our investment in Regulus. Our maximum exposure to loss related to our variable interest entities is limited to the carrying value of our investments.

Accumulated other comprehensive (loss) income

Accumulated other comprehensive (loss) income is comprised of unrealized gains and losses on investments, net of taxes, and adjustments we made to reclassify realized gains and losses on investments from other accumulated comprehensive (loss) income to our condensed consolidated statement of operations. The following table summarizes changes in accumulated other comprehensive (loss) income for the three and nine months ended September 30, 2015 and 2014 (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2015	2014	2015	2014
Beginning balance accumulated other comprehensive income	$ 18,411	$ 24,719	$ 39,747	$ 21,080
Unrealized losses on securities, net of tax (1)	(16,157)	(6,994)	(37,493)	(3,189)
Amounts reclassified from accumulated other comprehensive (loss) income (2)	(20,211)	(831)	(20,211)	(997)
Net other comprehensive loss for the period	(36,368)	(7,825)	(57,704)	(4,186)
Ending balance accumulated other comprehensive (loss) income	$ (17,957)	$ 16,894	$ (17,957)	$ 16,894

(1) Other comprehensive loss for the three months ended September 30, 2014 included income tax benefit of $2.5 million. There was no tax expense or benefit for the three and nine months ended September 30, 2015 and the nine months ended September 30, 2014.

(2) Amounts for the three and nine months ended September 30, 2015 are included in gain on investment in Regulus Therapeutics Inc. on our condensed consolidated statement of operations. For the three and nine months ended September 30, 2014, $0.5 million is included in the gain on investment in Regulus Therapeutics Inc., with the remaining amount included in gain on investments, net on our condensed consolidated statement of operations.

Convertible debt

We account for convertible debt instruments, including our 1 percent and 2¾ percent notes, that may be settled in cash upon conversion (including partial cash settlement) by separating the liability and equity components of the instruments in a manner that reflects our nonconvertible debt borrowing rate. We determine the carrying amount of the liability component by measuring the fair value of similar debt instruments that do not have the conversion feature. If no similar debt instrument exists, we estimate fair value by using assumptions that market participants would use in pricing a debt instrument, including market interest rates, credit standing, yield curves and volatilities. Determining the fair value of the debt component requires the use of accounting estimates and assumptions. These estimates and assumptions are judgmental in nature and could have a significant impact on the determination of the debt component, and the associated non-cash interest expense.

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 resulted in us recording our debt at a discount. We are amortizing the debt discount over the life of the convertible notes as additional non-cash interest expense utilizing the effective interest method.

Segment information

In 2015, we began operating as two segments, our Isis Core segment, previously referred to as Drug Discovery and Development, and our new segment, Akcea Therapeutics, which includes the operations of our newly-formed and wholly-owned subsidiary, Akcea Therapeutics, Inc. We formed Akcea to develop and commercialize the drugs from our lipid franchise. We provide segment financial information and results for our Isis Core segment and our Akcea Therapeutics segment based on the segregation of revenues and expenses that our chief decision maker reviews to assess operating performance and to make operating decisions. We use judgments and estimates in determining the allocation of shared expenses to the two segments.

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 ESPP, based on the estimated fair value of the award on the date of grant. 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 our 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, 2015 and 2014, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Nine Months Ended September 30,	
	2015	2014
Risk-free interest rate	1.5%	1.6%
Dividend yield	0.0%	0.0%
Volatility	53.7%	50.7%
Expected life	4.5 years	4.6 years

ESPP:

	Nine Months Ended September 30,	
	2015	2014
Risk-free interest rate	0.1%	0.1%
Dividend yield	0.0%	0.0%
Volatility	51.7%	60.6%
Expected life	6 months	6 months

Board of Director Stock Options:

	Nine Months Ended September 30,	
	2015	2014
Risk-free interest rate	2.1 %	2.2 %
Dividend yield	0.0 %	0.0 %
Volatility	52.2 %	54.2 %
Expected life	6.9 years	6.9 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 board of directors for the nine months ended September 30, 2015 was $67.57 and $57.16 per share, respectively.

The following table summarizes stock-based compensation expense for the three and nine months ended September 30, 2015 and 2014 (in thousands), which was allocated as follows:

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2015	2014	2015	2014
Research, development and patent expenses	$ 11,297	$ 6,606	$ 32,248	$ 18,879
General and administrative	3,700	1,512	9,659	4,015
Total	$ 14,997	$ 8,118	$ 41,907	$ 22,894

Non-cash stock-based compensation expense was $15.0 million and $41.9 million for the three and nine months ended September 30, 2015, respectively, and increased compared to $8.1 million and $22.9 million for the same periods in 2014 primarily due to the increase in our stock price in January 2015 compared to January 2014. As of September 30, 2015, total unrecognized estimated non-cash stock-based compensation expense related to non-vested stock options and RSUs was $53.1 million and $20.2 million, respectively. We will adjust total unrecognized compensation cost for future changes in estimated forfeitures. We expect to recognize the cost of non-cash, stock-based compensation expense related to non-vested stock options and RSUs over a weighted average amortization period of 1.3 years and 1.4 years, respectively.

Amendments to equity plans

In June 2015, after receiving approval from our stockholders, we amended our 2011 Equity Incentive Plan and our 2002 Non-Employee Directors Stock Option Plan to increase the total number of shares reserved for issuance under each plan. We increased the shares available under our 2011 Equity Incentive Plan from 5.5 million to 11 million and we increased our 2002 Non-Employee Directors Stock Option Plan from 1.2 million to 2 million.

Impact of recently issued accounting standards

In May 2014, the FASB issued accounting guidance on the recognition of revenue from customers. Under this guidance, an entity will recognize revenue when it transfers promised goods or services to customers in an amount that reflects what the entity expects in exchange for the goods or services. This guidance also requires more detailed disclosures to enable users of the financial statements to understand the nature, amount, timing and uncertainty of revenue and cash flows arising from contracts with customers. The guidance as originally issued is effective for fiscal years, and interim periods within that year, beginning after December 15, 2016. In July 2015, the FASB issued updated accounting guidance to allow for an optional one year deferral from the original effective date. As a result, we can choose to adopt this guidance beginning January 1, 2017 or on January 1, 2018. The guidance allows us to select one of two methods of adoption, either the full retrospective approach, meaning the guidance would be applied to all periods presented, or modified retrospective, meaning the cumulative effect of applying the guidance would be recognized as an adjustment to our opening retained earnings balance. We are currently determining the adoption method and timing as well as the effects the adoption will have on our consolidated financial statements and disclosures.

In August 2014, the FASB issued accounting guidance on how and when to disclose going-concern uncertainties in the financial statements. This guidance will require us to perform interim and annual assessments to determine our ability to continue as a going concern within one year from the date that we issue our financial statements. The guidance is effective for fiscal years, and interim periods within that year, beginning after December 15, 2016. We will adopt this guidance in our fiscal year beginning January 1, 2017. We do not expect this guidance to have any effect on our consolidated financial statements.

In February 2015, the FASB issued accounting guidance which amends existing consolidation guidance for entities that are required to evaluate whether they should consolidate certain legal entities. The guidance is effective for fiscal years, and interim periods within that year, beginning after December 15, 2015. We will adopt this guidance in our fiscal year beginning January 1, 2016. We do not expect this guidance to have any effect on our consolidated financial statements.

In April 2015, the FASB issued accounting guidance to simplify the presentation of debt issuance costs. The amended guidance requires us to present debt issuance costs as a direct deduction from the carrying amount of the related debt liability rather than as an asset. The guidance does not require us to change how we recognize and measure our debt issuance costs. The guidance is effective for fiscal years, and interim periods within that year, beginning after December 15, 2015. We will adopt this guidance in our fiscal year beginning January 1, 2016. We do not expect this guidance to have a material impact on our consolidated financial statements.

In April 2015, the FASB issued accounting guidance to clarify the accounting for fees paid in cloud computing arrangements. The amendment provides guidance to customers about whether a cloud computing arrangement includes a software license element consistent with the acquisition of other software licenses or if the arrangement excludes a software license and should be accounted for as a service contract. The guidance does not change the accounting for service contracts. The guidance is effective for fiscal years, and interim periods within that year, beginning after December 15, 2015. We will adopt this guidance in our fiscal year beginning January 1, 2016 on a prospective basis. We do not expect this guidance to have a material impact on our consolidated financial statements.

In July 2015, the FASB issued accounting guidance to simplify the remeasurment of inventory. The amended guidance applies to entities that value inventory under methods other than last-in first-out (LIFO) or the retail inventory method and applies to us because we value our inventory under the FIFO method. The amended guidance requires us to measure our inventory at the lower of cost and net realizable value. The guidance is effective for fiscal years, and interim periods within that year, beginning after December 15, 2015 on a prospective basis. We will adopt this guidance in our fiscal year beginning January 1, 2016. We do not expect this guidance to have any effect on our consolidated financial statements.

3. Investments

As of September 30, 2015, 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, or 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, 2015:

One year or less	52%
After one year but within two years	28%
After two years but within three and a half years	20%
Total	100%

As illustrated above, at September 30, 2015, 80 percent of our available-for-sale securities had a maturity of less than two years.

All of our available-for-sale securities are available to us for use in our current operations. As a result, we categorize all of these securities as current assets even though the stated maturity of some individual securities may be one year or more beyond the balance sheet date.

At September 30, 2015, we had an ownership interest of less than 20 percent in one private company and two public companies with which we conduct business. The privately-held company is Atlantic Pharmaceuticals Limited and the publicly-traded companies are Antisense Therapeutics Limited and Regulus. We account for equity investments in the privately-held company 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 July 2015, we sold approximately 2.7 million shares of Regulus' common stock for total proceeds of $25.5 million, resulting in a $20.2 million gain, which we recognized in the third quarter of 2015. We remain a significant shareholder of Regulus' common stock.

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

September 30, 2015	Cost	Gross Unrealized Gains	Gross Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Available-for-sale securities (1):					
Corporate debt securities	$ 178,172	$ 37	$ (88)	$ —	$ 178,121
Debt securities issued by U.S. government agencies	91,609	8	(6)	—	91,611
Debt securities issued by states of the United States and political subdivisions of the states (2)	62,048	36	(59)	—	62,025
Total securities with a maturity of one year or less	331,829	81	(153)	—	331,757
Corporate debt securities	270,045	132	(701)	—	269,476
Debt securities issued by U.S. government agencies	30,654	19	(2)	—	30,671
Debt securities issued by states of the United States and political subdivisions of the states	61,388	28	(121)	—	61,295
Total securities with a maturity of more than one year	362,087	179	(824)	—	361,442
Total available-for-sale securities	$ 693,916	$ 260	$ (977)	$ —	$ 693,199
Equity securities:					
Regulus Therapeutics Inc.	$ 7,162	$ 11,432	$ —	$ —	$ 18,594
Securities included in other current assets	880	—	—	(880)	—
Total equity securities	$ 8,042	$ 11,432	$ —	$ (880)	$ 18,594
Total available-for-sale and equity securities	$ 701,958	$ 11,692	$ (977)	$ (880)	$ 711,793

December 31, 2014	Cost	Gross Unrealized Gains	Gross Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Available-for-sale securities (1):					
Corporate debt securities (2)	$ 219,856	$ 89	$ (89)	$ —	$ 219,856
Debt securities issued by U.S. government agencies	47,496	7	(27)	—	47,476
Debt securities issued by the U.S. Treasury (2)	19,008	9	—	—	19,017
Debt securities issued by states of the United States and political subdivisions of the states (2)	45,196	19	(53)	—	45,162
Total securities with a maturity of one year or less	331,556	124	(169)	—	331,511
Corporate debt securities	152,730	16	(600)	—	152,146
Debt securities issued by U.S. government agencies	62,530	—	(151)	—	62,379
Debt securities issued by states of the United States and political subdivisions of the states	60,073	32	(234)	—	59,871
Total securities with a maturity of more than one year	275,333	48	(985)	—	274,396
Total available-for-sale securities	$ 606,889	$ 172	$ (1,154)	$ —	$ 605,907
Equity securities:					
Regulus Therapeutics Inc.	$ 12,477	$ 69,404	$ —	$ —	$ 81,881
Securities included in other current assets	880	—	—	(880)	—
Total equity securities	$ 13,357	$ 69,404	$ —	$ (880)	$ 81,881
Total available-for-sale and equity securities	$ 620,246	$ 69,576	$ (1,154)	$ (880)	$ 687,788

(1) Our available-for-sale securities are held at amortized cost.

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

Investments we considered to be temporarily impaired at September 30, 2015 were as follows (in thousands):

	Number of Investments	Less than 12 months of temporary impairment		More than 12 months of temporary impairment		Total temporary impairment	
		Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses
Corporate debt securities	247	$ 293,774	$ (773)	$ 9,421	$ (16)	$ 303,195	$ (789)
Debt securities issued by U.S. government agencies	7	40,497	(8)	—	—	40,497	(8)
Debt securities issued by states of the United States and political subdivisions of the states	96	50,648	(72)	14,899	(108)	65,547	(180)
Total temporarily impaired securities	350	$ 384,919	$ (853)	$ 24,320	$ (124)	$ 409,239	$ (977)

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

4. Fair Value Measurements

We use a three-tier fair value hierarchy to prioritize the inputs used in our fair value measurements. These tiers include: Level 1, defined as observable inputs such as quoted prices in active markets for identical assets, which includes our money market funds and treasury securities classified as available-for-sale securities and our investment in equity securities in publicly-held biotechnology companies; Level 2, defined as inputs other than quoted prices in active markets that are either directly or indirectly observable, which includes our fixed income securities and commercial paper classified as available-for-sale securities; and Level 3, defined as unobservable inputs in which little or no market data exists, therefore requiring us to develop our own assumptions. Our Level 3 investments include our investments in the equity securities of publicly-held biotechnology companies for which we calculated a lack of marketability discount because there were restrictions on when we could trade the securities. We determine 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. The majority of our securities have been classified as Level 2. We obtain the fair value of our Level 2 investments from our custodian bank 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 banks or professional pricing service provider and comparing that fair value to the fair value based on observable market prices. During the nine months ended September 30, 2015, there were no transfers between our Level 1 and Level 2 investments. We recognize transfers between levels of the fair value hierarchy on the date of the event or change in circumstances that caused the transfer.

We measure the following major security types at fair value on a recurring basis. The following summary breaks down the fair-value hierarchy that we used to value each security at September 30, 2015 and December 31, 2014 (in thousands):

	At September 30, 2015	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 114,602	$ 114,602	$ —	$ —
Corporate debt securities (2)	447,597	—	447,597	—
Debt securities issued by U.S. government agencies (2)	122,282	—	122,282	—
Debt securities issued by states of the United States and political subdivisions of the states (3)	123,320	—	123,320	—
Investment in Regulus Therapeutics Inc.	18,594	18,594	—	—
Total	$ 826,395	$ 133,196	$ 693,199	$ —

	At December 31, 2014	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 104,680	$ 104,680	$ —	$ —
Corporate debt securities (4)	372,002	—	372,002	—
Debt securities issued by U.S. government agencies (2)	109,855	—	109,855	—
Debt securities issued by the U.S. Treasury (5)	19,017	19,017	—	—
Debt securities issued by states of the United States and political subdivisions of the states (6)	105,033	—	105,033	—
Investment in Regulus Therapeutics Inc.	81,881	—	—	81,881
Total	$ 792,468	$ 123,697	$ 586,890	$ 81,881

(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) $7.6 million included in cash and cash equivalents on our condensed consolidated balance sheet, with the difference included in short-term investments on our condensed consolidated balance sheet.

(4) $0.8 million included in cash and cash equivalents on our condensed consolidated balance sheet, with the difference included in short-term investments on our condensed consolidated balance sheet.

(5) $10 million included in cash and cash equivalents on our condensed consolidated balance sheet, with the difference included in short-term investments on our condensed consolidated balance sheet.

(6) $9.3 million included in cash and cash equivalents on our condensed consolidated balance sheet, with the difference included in short-term investments on our condensed consolidated balance sheet.

In November 2014, Regulus completed a public offering. As part of the offering, we sold shares of Regulus' common stock and became subject to trading restrictions on our remaining shares through January 2015. Therefore, at December 31, 2014, we recorded a lack of marketability discount on our investment in Regulus and classified it as a Level 3 investment. At the end of January 2015, we reclassified our investment in Regulus to a Level 1 investment because the contractual trading restrictions on the shares we own ended.

The following is a reconciliation of our investments measured at fair value on a recurring basis using significant unobservable inputs (Level 3) for the nine months ended September 30, 2015 (in thousands):

Beginning balance of Level 3 investments (at December 31, 2014)	$ 81,881
Total gain included in accumulated other comprehensive income (loss)	22,377
Transfers out of Level 3 investments	(104,258)
Ending balance of Level 3 investments (at September 30, 2015)	$ —

Other Fair Value Disclosures

Our 1 percent and 2¾ percent notes had a fair value of $454.6 million and $149.4 million, respectively at September 30, 2015. We determine the fair value of our notes based on quoted market prices for these notes, which are Level 2 measurements because the notes do not trade regularly.

5. Line of Credit Arrangement

In June 2015, we entered into a five-year revolving line of credit agreement with Morgan Stanley Private Bank, National Association, or Morgan Stanley. Under the credit agreement, we can borrow up to a maximum of $20 million of revolving credit for general working capital purposes. Under the credit agreement interest is payable monthly in arrears on the outstanding principal at a rate based on our option of:

(i) a floating rate equal to the one-month London Interbank Offered Rate, or LIBOR, in effect plus 1.25 percent per annum;
(ii) a fixed rate equal to LIBOR plus 1.25 percent for a period of one, two, three, four, six, or twelve months as elected by us; or
(iii) a fixed rate equal to the LIBOR swap rate during the period of the loan.

Additionally, we will pay 0.25 percent per annum, payable quarterly in arrears, for any amount unused under the credit facility beginning after June 2016. We did not have any outstanding borrowings under the credit facility as of September 30, 2015.

The credit agreement includes customary affirmative and negative covenants and restrictions. We were in compliance with all covenants of the credit agreement as of September 30, 2015.

6. Collaborative Arrangements and Licensing Agreements

Traditional Pharmaceutical Alliances and Licensing

AstraZeneca

Oncology Collaboration

In December 2012, we entered into a collaboration agreement with AstraZeneca to discover and develop antisense drugs against five cancer targets. As part of the agreement, we granted AstraZeneca an exclusive license to develop and commercialize ISIS-STAT3-2.5$_{Rx}$ and ISIS-AR-2.5$_{Rx}$ for the treatment of cancer and an option to license up to three anti-cancer drugs under a separate research program. Together with AstraZeneca we are evaluating ISIS-STAT3-2.5Rx in patients with advanced cancer. AstraZeneca is conducting a clinical study of ISIS-STAT3-2.5$_{Rx}$ in patients with advanced metastatic hepatocellular carcinoma, or HCC. We are conducting a clinical study evaluating ISIS-STAT3-2.5$_{Rx}$ 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 global development, regulatory and commercialization activities for ISIS-STAT3-2.5$_{Rx}$. In June 2013, we and AstraZeneca added a second development candidate, ISIS-AR-2.5$_{Rx}$, to our collaboration. ISIS-AR-2.5$_{Rx}$ is an antisense drug we designed to treat patients with prostate cancer by inhibiting the production of the androgen receptor, or AR. AstraZeneca is currently evaluating ISIS-AR-2.5$_{Rx}$ in a Phase 1/2 study in patients with AR-related cancers. AstraZeneca is responsible for all other global development, regulatory and commercialization activities for ISIS-AR-2.5$_{Rx}$. In addition, we are responsible for identifying a development candidate for each of the three anti-cancer research programs. AstraZeneca has the option to license drugs resulting from each of the three anti-cancer research programs, and if AstraZeneca exercises its option for a drug, it will be responsible for all further global development, regulatory and commercialization activities for such drug.

Under the terms of the agreement, we received $31 million comprised of a $25 million upfront payment we received in December 2012 and a $6 million payment we received in June 2013. We recorded revenue of $11.5 million upon receipt of these payments and we have amortized $11.9 million into revenue as we have performed development activities under this collaboration. We are recognizing the remaining $7.6 million related to the option to license three drugs under the research program through December 2016.

In October 2014, we and AstraZeneca amended our agreement for ISIS-STAT3-2.5$_{Rx}$. Under the amended terms of the agreement, we received a $7.5 million milestone payment in November 2014 from AstraZeneca for advancing ISIS-STAT3-2.5$_{Rx}$ in patients with advanced cancers. Upon AstraZeneca's initiation of a Phase 2 study, we will earn a $17.5 million milestone payment.

We are eligible to receive milestone payments and license fees from AstraZeneca as programs advance in development. In addition, we are eligible to receive tiered royalties up to the low to mid-teens on any product sales of drugs resulting from these programs. If AstraZeneca successfully develops ISIS-STAT3-2.5$_{Rx}$, ISIS-AR-2.5$_{Rx}$, and the three drugs under the research program, we could receive substantive milestone payments of more than $858 million, including up to $238 million for the achievement of development milestones and up to $620 million for the achievement of regulatory milestones. From inception through September 2015, we have received $63.5 million in payments under these collaboration programs. We will earn the next milestone payment of $10 million if we designate a development candidate for a cancer drug under our research program with AstraZeneca.

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 collaboration program. If AstraZeneca exercises its option, it will be responsible for all further global development, regulatory and commercialization activities for such drug. We received a $0.8 million upfront payment, which we are amortizing through December 2016. We are eligible to receive license fees and substantive milestone payments of $163.2 million, including up to $45.3 million for the achievement of research and development milestones and up to $105 million for regulatory milestones. From inception through September 2015, we have received $0.8 million in payments under this collaboration program. We will earn the next $3.3 million milestone payment if AstraZeneca selects a development candidate under this collaboration. In addition, we are eligible to receive tiered royalties up to the low teens on sales from any product that AstraZeneca successfully commercializes under this collaboration program.

Cardiometabolic and Renal Diseases Collaboration

In July 2015, we and AstraZeneca formed a strategic collaboration to discover and develop antisense therapies for treating cardiovascular and metabolic diseases, primarily focused on targets in the kidney, and renal diseases. As part of the agreement, we granted AstraZeneca an exclusive license to a preclinical program and the option to license a drug for each target advanced under this research collaboration. Upon acceptance of a drug development candidate, AstraZeneca will be responsible for all further global development, regulatory and commercialization activities for such drug. Under the terms of the agreement, we received a $65 million upfront payment. Since this agreement has multiple elements, we evaluated the deliverables in this arrangement and determined that none of the deliverables have stand-alone value because of the early stage of research for this collaboration. Therefore, we concluded there is one unit of accounting and we are amortizing the $65 million upfront payment through August 2021. We are eligible to receive license fees and substantive milestone payments of up to more than $4 billion, including up to $1.1 billion for the achievement of development milestones and up to $2.9 billion for regulatory milestones. We will earn the next milestone payment of $25 million under this collaboration upon identification of the first drug candidate to move into development. In addition, we are eligible to receive tiered royalties up to the low teens on sales from any product that AstraZeneca successfully commercializes under this collaboration agreement.

Each of our agreements with AstraZeneca will continue until the expiration of all payment obligations under the applicable agreement. In addition, the agreement, or any program under the applicable agreement, may terminate early under the following situations:

- AstraZeneca may terminate the agreement or any program at any time by providing written notice to us;
- AstraZeneca may terminate the agreement or any program by providing written notice if we undergo a change of control with a third party; and
- Either we or AstraZeneca may terminate the agreement or any program by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement, or the entire agreement if the other party becomes insolvent.

During the three and nine months ended September 30, 2015, we earned revenue of $1.5 million and $3.0 million, respectively, from our relationship with AstraZeneca. In comparison, we earned $0.6 million and $19.7 million for the same periods in 2014. Our condensed consolidated balance sheet at September 30, 2015 included deferred revenue of $66.7 million related to our relationship with AstraZeneca.

Bayer

In May 2015, we entered into an exclusive license agreement with Bayer to develop and commercialize ISIS-FXI$_{Rx}$ for the prevention of thrombosis. We are responsible for completing ongoing development activities. Bayer is responsible for all other development and commercialization activities for ISIS-FXI$_{Rx}$.

Under the terms of the agreement, we are eligible to receive $155 million in near-term payments, including a $100 million upfront payment we received in the second quarter of 2015 and a $55 million milestone payment that we are eligible to receive upon advancement of the program following a Phase 2 study in patients with compromised kidney function. We recorded revenue of $91.2 million related to the license for ISIS-FXI$_{Rx}$ in June 2015 and we are recognizing the remaining $8.8 million related to the ongoing development activities for ISIS-FXI$_{Rx}$ through July 2016.

Over the term of the agreement, we are eligible to receive up to $375 million in license fees, substantive milestone payments and other payments, including up to $120 million for the achievement of development milestones and up to $110 million for the achievement of commercialization milestones. In addition, we are eligible to receive tiered royalties in the low to high 20 percent range on gross margins of ISIS-FXI$_{Rx}$. We will earn the next milestone payment of $55 million upon the advancement of the program following an ongoing Phase 2 study of ISIS-FXI$_{Rx}$ in patients with compromised kidney function.

Our agreement with Bayer will continue until the expiration of all payment obligations under the agreement. In addition, the agreement, or any program under the agreement, may terminate early under the following situations:

- Bayer may terminate the agreement or any program at any time by providing written notice to us;
- Either we or Bayer may terminate the agreement or any program by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement, or the entire agreement if the other party becomes insolvent.

During the three and nine months ended September 30, 2015, we earned revenue of $1.0 million and $92.4 million, respectively, from our relationship with Bayer, which represented 2 percent and 40 percent, respectively, of our total revenue for those periods. Our condensed consolidated balance sheet at September 30, 2015 included deferred revenue of $7.6 million related to our relationship with Bayer.

Biogen

We have established four strategic collaborations with Biogen focused on using antisense technology to advance the treatment of neurological and neuromuscular disorders. These collaborations combine our expertise in creating antisense drugs to evaluate potential neurological targets with Biogen's expertise in developing therapies for neurological disorders. We and Biogen are developing four drugs to treat neurological disorders under these collaborations, including nusinersen, ISIS-DMPK-2.5$_{Rx}$, and two drugs to treat undisclosed neurodegenerative diseases, ISIS-BIIB3$_{Rx}$ and ISIS-BIIB4$_{Rx}$. In addition to these four drugs, we and Biogen are evaluating numerous additional targets for the development of drugs to treat neurological disorders.

Nusinersen (formerly ISIS-SMN$_{Rx}$)

In January 2012, we entered into a collaboration agreement with Biogen to develop and commercialize nusinersen for the treatment of SMA. We are currently conducting a Phase 3 study evaluating nusinersen in infants with SMA and a Phase 3 study evaluating nusinersen in children with SMA. Patients from both of the Phase 3 studies continue to have access to nusinersen through our Phase 3 open-label extension study. In addition, we are evaluating nusinersen in two Phase 2 open-label, multiple-dose, dose-escalation studies, one in children with SMA and one in infants with SMA. Patients from both of the Phase 2 studies continue to have access to nusinersen through open-label extension dosing. We are responsible for completing the Phase 2 and Phase 3 trials we are currently conducting. Biogen has the option to license nusinersen. If Biogen exercises its option, it will pay us a license fee and will assume all other global development, regulatory and commercialization responsibilities. Biogen may exercise this option upon completion of and data review of the first successful Phase 2/3 trial or completion of both Phase 2/3 trials. An amendment in December 2014 provided for additional opt-in scenarios, based on the filing or the acceptance of a new drug application or marketing authorization application with the FDA or EMA. In June 2015, we and Biogen amended the development plan for nusinersen to include conducting the open-label extension study for the Phase 3 studies in infants and children. As a result of the change to the development plan, we earned an $11 million milestone payment when we initiated the Phase 3 open-label extension study and we are eligible to earn additional milestone and other payments.

Under the terms of the agreement, we received an upfront payment of $29 million, which we are amortizing through February 2017. We are also eligible to receive a license fee, milestone payments and tiered royalties up to the mid-teens on any product sales of nusinersen. Under the terms of the amended agreement, we are eligible to receive up to $346 million in a license fee and payments, including up to $121 million in substantive milestone and other payments associated with the clinical development of nusinersen prior to licensing and up to $150 million in substantive milestone payments if Biogen achieves pre-specified regulatory milestones. In the first nine months of 2015, we earned $26.7 million for advancing the studies we are conducting in infants and children with SMA. From inception through September 2015, we have received over $120 million in payments for advancing nusinersen, not including an $11 million milestone payment we earned in October 2015 for initiating the open-label extension study of nusinersen for the Phase 3 studies in infants and children. We will earn the next milestone payment of $2 million if we further advance the Phase 3 study of nusinersen in children.

ISIS-DMPK-2.5$_{Rx}$

In June 2012, we and Biogen entered into a second and separate collaboration agreement to develop and commercialize a novel antisense drug, ISIS-DMPK-2.5$_{Rx}$, targeting DMPK for the treatment of DM1. We are responsible for global development of the drug through the completion of the first Phase 2 clinical trial. Biogen has the option to license the drug through the completion of the first Phase 2 trial. If Biogen exercises its option, it will assume all other global development, regulatory and commercialization responsibilities. Under the terms of the agreement, we received an upfront payment of $12 million, which we are amortizing through October 2018. In June 2015, we and Biogen amended the development plan for ISIS-DMPK-2.5$_{Rx}$ under which we are eligible to earn additional milestone payments of up to $4.2 million for further advancing the Phase 1/2a study of ISIS-DMPK-2.5$_{Rx}$. Over the term of the collaboration, we are eligible to receive up to $263 million in a license fee and substantive milestone payments, including up to $63 million in development milestone payments and up to $130 million in milestone payments if Biogen achieves pre-specified regulatory milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on any product sales of the drug. From inception through September 2015, we have received $36 million in payments for advancing ISIS-DMPK-2.5$_{Rx}$. We will earn the next milestone payment of $2.8 million if we further advance the Phase 1/2a study for ISIS-DMPK-2.5$_{Rx}$ and we will earn a $35 million milestone payment if we initiate a Phase 2 study for ISIS-DMPK-2.5$_{Rx}$.

Neurology

In December 2012, we and Biogen entered into a third and separate collaboration agreement to develop and commercialize novel antisense drugs to three targets to treat neurological or neuromuscular diseases. We are responsible for the development of each of the drugs through the completion of the initial Phase 2 clinical study for such drug. Biogen has the option to license a drug from each of the three programs through the completion of the first Phase 2 study for each program. If Biogen exercises its option for a drug, it will assume all further global development, regulatory and commercialization responsibilities for that drug. Under the terms of the agreement, we received an upfront payment of $30 million, which we are amortizing through December 2020. Over the term of the collaboration, we are eligible to receive up to $259 million in a license fee and substantive milestone payments per program. We are eligible to 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. We are also eligible to receive up to $130 million in milestone payments per program if Biogen achieves pre-specified regulatory milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on any product sales of drugs resulting from each of the three programs. In February 2015, we earned a $10 million milestone payment when we initiated an IND-enabling toxicology study of ISIS-BIIB4$_{Rx}$, a drug for an undisclosed target designed to treat a neurodegenerative disease. From inception through September 2015, we have received $40 million in payments under this collaboration. We will earn the next milestone payment of $3 million for the continued development of an undisclosed target under this collaboration.

Strategic Neurology

In September 2013, we and Biogen entered into a fourth and separate collaboration agreement, 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 gained 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 through September 2019, and may be extended for any drug development programs being pursued under the collaboration. We will usually be responsible for drug discovery and early development of antisense drugs and Biogen will have the option to license antisense drugs after Phase 2 proof of concept. If Biogen exercises its option for a drug, it will assume all further global development, regulatory and commercialization responsibilities for that drug. Biogen will be responsible for all of the drug discovery and development activities for drugs using other modalities.

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. If we have a change of control during the first six years of the collaboration, we may be required to refund Biogen 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 are amortizing the $100 million upfront payment through September 2019. 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 could potentially require us to refund.

For each antisense molecule that is chosen for drug discovery and development under this collaboration, we are eligible to receive up to approximately $260 million in a license fee and substantive milestone payments. We are eligible to receive up to approximately $60 million for the achievement of research and development milestones, including amounts related to the cost of clinical trials, and up to $130 million for the achievement of regulatory milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on any product sales of antisense drugs developed under this collaboration. If other modalities are chosen, such as small molecules or monoclonal antibodies, we are eligible to receive up to $90 million in substantive milestone payments, including up to $35 million for the achievement of research and development milestones and up to $55 million for the achievement of regulatory milestones. In addition, we are eligible to receive tiered single-digit royalties on any product sales of drugs using non-antisense modalities developed under this collaboration. From inception through September 2015, we have received $135 million in payments under this collaboration. In April 2015, we earned a $10 million milestone payment for validating a fourth target under this collaboration. We will earn the next milestone payment of up to $10 million if we choose another target to advance under this collaboration.

Each of our agreements with Biogen will continue until the earlier of the date all of Biogen's options to obtain the exclusive licenses under the applicable agreement expire unexercised or, if Biogen exercises its option, until the expiration of all payment obligations under the applicable agreement. In addition, each agreement, or any program under an agreement, may terminate early under the following situations:

- Biogen may terminate the agreement or any program at any time by providing written notice to us;
- Under specific circumstances, if we are acquired by a third party with a product that directly competes with a compound being developed under the agreement, Biogen may terminate the affected program by providing written notice to us;
- If, within a specified period of time, any required clearance of a transaction contemplated by an agreement under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, is not received, then either we or Biogen may terminate the affected program by providing written notice to the other party; and
- Either we or Biogen may terminate any program by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement with respect to the affected program, or the entire agreement if the other party becomes insolvent.

During the three and nine months ended September 30, 2015, we earned revenue of $18.1 million and $75.1 million, respectively, from our relationship with Biogen, which represented 37 percent and 32 percent, respectively, of our total revenue for those periods. In comparison, we earned revenue of $31.7 million and $76.4 million for the same periods in 2014. Our condensed consolidated balance sheet at September 30, 2015 included deferred revenue of $98.1 million related to our relationship with Biogen.

GSK

In March 2010, we entered into a strategic alliance with GSK using 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. Our strategic alliance currently includes five drugs in development. GSK has the exclusive option to license drugs resulting from this alliance at Phase 2 proof-of-concept for a license fee. If GSK exercises its exclusive option for any drugs resulting from this alliance, it will be responsible for all further global development, regulatory and commercialization activities for such drug. Under the terms of the agreement, we received $38 million in upfront and expansion payments, which we are amortizing through March 2017.

In October 2012, we and GSK amended the original agreement to reflect an accelerated clinical development plan for ISIS-TTR_{Rx}. From inception through September 2015, we have earned $60 million, primarily in milestone payments, from GSK related to the development of ISIS-TTR_{Rx}. We are also eligible to earn an additional $10 million pre-licensing milestone payment associated with the ISIS-TTR_{Rx} Phase 2/3 study. In addition, under the amended agreement, we and GSK increased the regulatory and commercial milestone payments we can earn should ISIS-TTR_{Rx} receive marketing approval and meet pre-agreed sales targets. In September 2015, we and GSK amended the development plan for ISIS-TTR_{Rx} to support the Phase 3 cardiomyopathy study, which GSK will conduct.

In addition to ISIS-TTR_{Rx}, we have four drugs in development. We are developing ISIS-HBV_{Rx}, an antisense drug designed to reduce the production of viral proteins associated with hepatitis B virus, or HBV infection. We are also developing ISIS-GSK4-L_{Rx} and ISIS-RHO-2.5_{Rx}, which are antisense drugs we designed to treat ocular diseases. In addition, we are developing a drug to treat an undisclosed target, ISIS-GSK6-L_{Rx}.

Under our agreement, if GSK successfully develops all five drugs for one or more indications and achieves pre-agreed sales targets, we could receive license fees and substantive milestone payments of more than $1.3 billion, including up to $223.5 million for the achievement of development milestones, up to $483.5 million for the achievement of regulatory milestones and up to $428 million for the achievement of commercialization milestones. Through September 2015, we have received $129.5 million in payments under this strategic alliance with GSK, not including a $5 million milestone payment we earned in October when we initiated a Phase 1 study of ISIS-GSK4-L_{Rx}. We will earn the next milestone payment of $1.5 million if we further advance a program under this collaboration. In addition, we are eligible to receive tiered royalties up to the mid-teens on sales from any product that GSK successfully commercializes under this alliance.

Our alliance with GSK will continue until the earlier of the date that all of GSK's options to obtain the exclusive licenses under the agreement expire unexercised or, if GSK exercises its option, until the expiration of all payment obligations under the agreement. In addition, the agreement, or any program under the agreement, may terminate early under the following situations:

- GSK may terminate any program, other than the ISIS-TTR_{Rx} program, at any time by providing written notice to us;
- GSK may terminate the ISIS-TTR_{Rx} program by providing written notice to us after reviewing specific data from the Phase 3 study for the program; and
- Either we or GSK may terminate any program by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement with respect to the affected program, or the entire agreement if the other party becomes insolvent.

During the three and nine months ended September 30, 2015, we earned revenue of $1.6 million and $22.4 million, respectively, from our relationship with GSK. In comparison, we earned revenue of $5.1 million and $11.9 million for the same periods in 2014. Our condensed consolidated balance sheet at September 30, 2015 included deferred revenue of $5.5 million 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 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. If Roche exercises its option, it will be responsible for global development, regulatory and commercialization activities for any drug arising out of the collaboration. We are also working collaboratively with Roche on the discovery of an antisense drug utilizing Roche's "brain shuttle" program. Under the terms of the agreement, we received an upfront payment of $30 million in April 2013, which we are amortizing through January 2017. We are eligible to receive up to $362 million in a license fee and substantive milestone payments including up to $67 million for the achievement of development milestones, up to $170 million for the achievement of regulatory milestones and up to $80 million for the achievement of commercialization milestone payments. In addition, we are eligible to receive up to $136.5 million in milestone payments for each additional drug successfully developed and up to $50 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 up to the mid-teens on any product sales of drugs resulting from this alliance. Through September 2015, we have received $52 million in payments under this strategic alliance with Roche, including the $22 million milestone payment we earned in July 2015 when we initiated a Phase 1/2 study of ISIS-HTT_{Rx}. We will earn the next milestone payment of $10 million if we initiate a Phase 2 trial for ISIS-HTT_{Rx}.

Our alliance with Roche will continue until the earlier of the date Roche's option to obtain the exclusive license under the agreement expires unexercised or, if Roche exercises its option, until the expiration of all payment obligations under the agreement. In addition, the agreement may terminate early under the following situations:

- Roche may terminate the agreement at any time by providing written notice to us;
- Either we or Roche may terminate the agreement by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement or if the other party becomes insolvent; and
- Either we or Roche may terminate the brain shuttle program if at least one development candidate is not designated under such program by a mutually agreed deadline.

During the three and nine months ended September 30, 2015, we earned revenue of $24.2 million and $29.0 million, respectively, from our relationship with Roche. In comparison, we earned $2.3 million and $6.7 million for the same periods in 2014. Our condensed consolidated balance sheet at September 30, 2015 included deferred revenue of $10.9 million related to our relationship with Roche.

7. Segment Information and Concentration of Business Risk

In 2015, we began reporting our financial results in two reportable segments, Isis Core, previously referred to as Drug Discovery and Development, and Akcea Therapeutics, our new wholly owned subsidiary. Segment loss from operations includes revenue less operating expenses attributable to each segment.

In our Isis Core segment we are exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class or best-in-class drugs for us and our partners. Our Isis Core segment generates revenue from a multifaceted partnering strategy.

We established Akcea to develop and commercialize the drugs from our lipid franchise. Moving our lipid drugs into a company that we own and control ensures that our core focus at Isis remains on innovation while allowing us to maintain control over and retain more value from our lipid drugs. To date, Akcea has not earned any revenue.

The following is our segment information for the three and nine months ended September 30, 2015 (in thousands).

Three Months Ended September 30, 2015	Isis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Research and development	$ 52,104	$ —	$ (3,186)	$ 48,918
Licensing and royalty	203	—	—	203
Total segment revenue	$ 52,307	$ —	$ (3,186)	$ 49,121
Loss from operations	$ (33,517)	$ (14,621)	$ —	$ (48,138)

Nine Months Ended September 30, 2015	Isis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Research and development	$ 233,655	$ —	$ (3,186)	$ 230,469
Licensing and royalty	1,664	—	—	1,664
Total segment revenue	$ 235,319	$ —	$ (3,186)	$ 232,133
Loss from operations	$ 17,840	$ (30,661)	$ —	$ (12,821)

The following is our segment information for the three and nine months ended September 30, 2014 (in thousands) revised for comparative purposes to show operating costs for Akcea-related projects in 2014:

Three Months Ended September 30, 2014	Isis Core	Akcea Therapeutics	Total
Revenue:			
Research and development	$ 43,798	$ —	$ 43,798
Licensing and royalty	265	—	265
Total segment revenue	$ 44,063	$ —	$ 44,063
Loss from operations	$ (14,886)	$ (6,607)	$ (21,493)

Nine Months Ended September 30, 2014	Isis Core	Akcea Therapeutics	Total
Revenue:			
Research and development	$ 119,975	$ —	$ 119,975
Licensing and royalty	9,325	—	9,325
Total segment revenue	$ 129,300	$ —	$ 129,300
Loss from operations	$ (41,609)	$ (16,202)	$ (57,811)

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,	
	2015	2014	2015	2014
Partner A	49 %	5 %	12 %	5 %
Partner B	37 %	72 %	32 %	59 %
Partner C	3 %	12 %	10 %	9 %
Partner D	2 %	0 %	40 %	0 %

Contracts receivables from three significant partners comprised approximately 96 percent and 99 percent of our contracts receivables at September 30, 2015 and December 31, 2014, respectively.

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 wholly owned subsidiary, Akcea Therapeutics, Inc.

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 business of Akcea, our subsidiary, the therapeutic and commercial potential of our technologies and drugs, including KYNAMRO, volanesorsen (formerly ISIS-APOCIII$_{Rx}$), nusinersen and ISIS-TTR$_{Rx}$, and other 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, 2014, which is on file with the U.S. Securities and Exchange Commission and are available from us, and those identified within this Item in the section entitled "Risk Factors" beginning on page 33 of this Report.

Overview

We are the leading company in RNA-targeted drug discovery and development, exploiting a proven novel drug discovery platform we created to generate a broad pipeline of first-in-class or best-in-class 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 with an emphasis on cardiovascular, metabolic, severe and rare diseases, including neurological disorders, and cancer. The efficiency of our drug discovery technology allows us to employ a unique business strategy designed to maximize the value of our drugs and technology while maintaining an effective cost structure that limits our cash needs. Our business strategy is supported by our platform technology, our robust pipeline of drugs and our diverse partnering strategies, which have enabled us to focus on doing what we do best – to discover and develop novel antisense drugs.

We have created a mature and broad pipeline of 38 drugs in development that represents the potential for significant commercial opportunities in many therapeutic areas. We have a number of drugs in later-stage development that we believe represent significant near-term commercial opportunities, including three drugs in Phase 3 trials, ISIS-TTR$_{Rx}$, nusinersen and volanesorsen. We designed these drugs to treat patients with severe and rare diseases who have very limited or no therapeutic options. ISIS-TTR$_{Rx}$ is designed to treat patients with transthyretin amyloidosis, or TTR amyloidosis, a fatal genetic disease in which patients experience progressive buildup of amyloid plaque deposits in tissues throughout the body, including peripheral nerves, heart, intestinal tract, kidney and bladder. ISIS-TTR$_{Rx}$ is currently in Phase 3 development to treat all forms of TTR amyloidosis, including the polyneuropathy and cardiomyopathy forms of the disease. Nusinersen is designed to treat patients with spinal muscular atrophy, or SMA, which is a severe motor-neuron disease that is the leading genetic cause of infant mortality. Volanesorsen is designed to treat patients with severely high triglyceride levels, including patients with a severe and rare genetic condition called familial chylomicronemia syndrome, or FCS and patients with partial lipodystrophy, another severe and rare genetic condition. The significant unmet medical need and the severity of these diseases could warrant a rapid path to market. Already this year, we have reported positive Phase 2 or open-label extension data on these three drugs, which, together with the safety profile we have reported for each, support continued development of these programs. We expect Phase 3 data in 2016/2017 for all three of these drugs, which may support regulatory filings for marketing approvals. We believe all of these drugs have the potential to reach the market in the next few years. We also have numerous drugs in our pipeline advancing in mid-stage clinical development that could represent significant near and mid-term licensing opportunities.

Our novel lipid-lowering product, KYNAMRO (mipomersen sodium) injection, is on the market in the United States for patients with HoFH. Patients with HoFH are at high cardiovascular risk and cannot reduce their LDL-C sufficiently with currently available lipid-lowering therapies. In January 2013, the FDA approved the marketing application for KYNAMRO for patients with HoFH. Genzyme, a Sanofi Company, has also obtained marketing

approval in other countries, and is pursuing marketing approval in multiple additional markets. We reported positive clinical results for KYNAMRO in a late-stage clinical study, FOCUS FH, in patients with severe HeFH in August 2015.

The efficiency and broad utility of our drug discovery technology supports the continued growth of our pipeline of antisense drugs. To maximize the value of our drugs and technologies, we have a multifaceted partnering strategy. Our partnering strategy provides us the flexibility to license each of our drugs at what we believe is the optimal time to maximize the near- and long-term value of our drugs. 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.

One component of our partnering strategy is to form traditional partnering alliances that enable us to discover and conduct early development of new drugs, outlicense our drugs to partners and build a base of license fees, milestone payments and profit share or royalty income. An example of this is our recent exclusive license of ISIS-FXI_{Rx} to Bayer to develop and commercialize ISIS-FXI_{Rx} for the prevention of thrombosis. As a leader in the antithrombotic market, Bayer has the expertise, resources and commitment to broadly develop ISIS-FXI_{Rx}. Bayer is preparing to conduct a robust development plan that represents a commitment to make a substantial investment in ISIS-FXI_{Rx}. Bayer is planning to focus on advancing ISIS-FXI_{Rx} to the market first for patients who have a high bleeding risk and as such are unable to take currently available antithrombotic agents, followed by a broader group of patients who are underserved by current anti-thrombotic treatments. Another example of our traditional partnering strategy was our license of KYNAMRO to Genzyme.

We also form preferred partner transactions that provide us with a vested partner 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. We benefit from this strategy because it allows us to expand and broaden our drug discovery efforts to new disease targets. We have formed preferred partner collaborations with the following companies:

- GSK - We are developing five drugs, including ISIS-TTR_{Rx}, which is in Phase 3 development.
- Janssen - We are discovering and developing antisense drugs that can be locally administered, including oral delivery, to treat autoimmune disorders in the gastrointestinal tract.
- Roche - We are discovering and developing antisense drugs to treat Huntington's disease.

In addition to our preferred partner collaborations, we have also built broad strategic relationships over time with Biogen and most recently with AstraZeneca.

- Biogen - We have four collaborations with Biogen to discover and develop antisense drugs to treat neurologic diseases, including nusinersen, which is in Phase 3 development. We currently have four drugs we are advancing through these collaborations, nusinersen, ISIS-DMPK-2.5_{Rx}, ISIS-$BIIB3_{Rx}$ and ISIS $BIIB4_{Rx}$. In addition to these four drugs, we and Biogen are evaluating numerous additional targets for the development of drugs to treat neurological disorders. Through our broad strategic partnership with Biogen, we are capitalizing on Biogen's extensive resources and expertise in neurological diseases to create a franchise of novel treatments for neurological disorders.
- AstraZeneca - We recently expanded our relationship with AstraZeneca with a strategic collaboration to discover and develop antisense drugs for cardiovascular, metabolic and renal diseases. The new collaboration builds on our broad existing relationship and supports AstraZeneca’s strategic approach in these therapeutic areas using novel RNA-targeted treatments. It also enables us to extend our use of our antisense technology to diseases of the kidney. This recent transaction adds to our existing collaboration to discover and develop antisense drugs to treat cancer and our drug delivery collaboration.

Similar to our other partnerships, we benefit financially from our preferred partner collaborations and our strategic collaborations from upfront payments, milestone payments, licensing fees and royalties.

Earlier this year, we established a wholly owned subsidiary, Akcea Therapeutics, Inc., to develop and commercialize the drugs from our lipid franchise, including volanesorsen, a Phase 3 drug in development to treat two severe and rare diseases; ISIS-APO(a)-L_{Rx}, the only drug in clinical development to selectively reduce Lp(a) for patients with high Lp(a); and ISIS-ANGPTL3-L_{Rx}, designed to be a broadly acting drug for mixed dyslipidemias and lipid disorders. To lead Akcea, we hired a senior business leader with commercialization expertise in severe and rare and cardiovascular diseases to maximize the value of our lipid franchise assets. Akcea has been building development and commercialization expertise in lipid and cardiometabolic diseases, and preparing for commercialization of volanesorsen, which is in Phase 3 development with data expected in late 2016/early 2017. Moving our lipid drugs into a company that we own and control ensures that our core focus at Isis remains on innovation while allowing us to maintain control over and retain more value from our lipid drugs.

We also work with a consortium of companies that can further develop our drugs and technology. We call these companies satellite companies. 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. For example, Regulus is a satellite company partner that we co-founded to discover and develop antisense drugs targeting microRNAs. Since 2014, we have received nearly $50 million from the sale of a portion of our Regulus stock and we remain a significant shareholder in the company. We also maintain our broad RNA technology leadership through collaborations with satellite companies. All of these different types of relationships are part of our partnering strategy, which we designed to maximize the value of our assets, minimize the development risks of a broad pipeline of novel new drugs, and provide us with significant reliable near-term revenue.

We have the potential to earn significant revenue from all of our partnerships. Since 2007, we have received more than $1.6 billion in cash from upfront and licensing fees, equity purchase payments, milestone payments and research and development funding from our partnerships. We have the potential to earn nearly $13 billion in future milestone payments and licensing fees from all of our partnerships. We also have the potential to share in the future commercial success of our inventions and drugs resulting from our partnerships through earn out, profit sharing, or royalty arrangements.

As an innovator in RNA-targeting drug discovery and development, we designed 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. Through September 2015, we have generated more than $420 million from our intellectual property sale and licensing program that helps support our internal drug discovery and development programs.

Recent Events *(2015 third quarter and subsequent activities)*

Corporate Highlights

- We and AstraZeneca formed a strategic collaboration to discover and develop antisense therapies for treating cardiovascular and metabolic diseases, primarily focused on targets in the kidney, and renal diseases. The collaboration enables us to broaden the application of our antisense technology to targets in the kidney.
  - In total, we have the potential to earn up to more than $4 billion in license fees and milestone payments.
    - We received a $65 million upfront payment from AstraZeneca and are eligible to earn substantial development and regulatory milestone payments and license fees. We are eligible to earn a payment of $25 million under this collaboration upon identification of the first drug candidate to move into development.
    - We are also eligible to earn tiered royalties up to the low teens on annual net sales for each of the programs.

Drug Development Highlights

- We reported positive clinical results from ISIS-APO(a)$_{Rx}$ and ISIS-APO(a)-L$_{Rx}$, ISIS-TTR$_{Rx}$ and KYNAMRO. These data exemplify the broad applicability and potential for antisense drugs to provide therapeutic benefit for many different diseases.
  - We and our subsidiary, Akcea Therapeutics, reported results from a Phase 2 study of ISIS-APO(a)$_{Rx}$ in patients with high lipoprotein(a), or Lp(a), a known driver of cardiovascular disease. In the Phase 2 study patients treated with ISIS-APO(a)$_{Rx}$ achieved reductions in Lp(a) of up to 94 percent. Data from this study were presented at the American Heart Association Scientific Sessions.
  - We and Akcea reported results from a Phase 1/2a, study of ISIS-APO(a)-L$_{Rx}$, a LIgand Conjugated Antisense (LICA) version of ISIS-APO(a)$_{Rx}$, in subjects with elevated Lp(a). In the Phase 1 study, subjects (with Lp(a) greater than 30 mg/dL) who received a single, low volume, subcutaneous injection of ISIS-APO(a)-L$_{Rx}$, achieved dose-dependent reductions in Lp(a) of up to 97 percent. Subjects who received multiple doses of ISIS-APO(a)-L$_{Rx}$ achieved up to 99 percent reduction in Lp(a) levels. In addition, ISIS-APO(a)-L$_{Rx}$ demonstrated the potential for a variety of convenient dose schedules- weekly, monthly, quarterly or less frequent dosing. This is the first clinical data from our LICA program and represents a greater than 30-fold increase in potency over ISIS-APO(a)$_{Rx}$, the non-LICA Lp(a) drug. These data significantly exceeded the potency and duration expectations predicted by preclinical experiments. Data from this study were presented at the American Heart Association Scientific Sessions.
  - Dr. Merrill Benson reported positive preliminary results from an ongoing Phase 2 study in patients with familial amyloid cardiomyopathy (FAC) and patients with wild-type transthyretin amyloidosis (wt-TTR amyloidosis, previously referred to as senile systemic amyloidosis, or SSA). In this open-label, investigator initiated study, after six and 12 months of treatment with ISIS-TTR$_{Rx}$, Dr. Benson observed:
    - Evidence of disease stabilization. These observations compare favorably to those from Benson's previously published natural history data, in which, disease progression was observed at 12 months.
    - Sustained reductions in TTR compared to baseline.
  - We reported positive results from an ongoing open-label extension study (OLE) of ISIS-TTR$_{Rx}$ in patients with familial amyloid polyneuropathy (FAP). An analysis conducted on the first 38 patients to reach at least three months of treatment in the OLE study showed a maximum reduction in TTR protein levels of up to 92 percent with a mean maximum (nadir) reduction of 76 percent as compared to patients' TTR levels at entry into the Phase 3 study.
  - We reported that the FOCUS FH study evaluating KYNAMRO in patients with severe heterozygous familial hypercholesterolemia met its primary efficacy endpoint with a statistically significant reduction of LDL-Cholesterol. We and Genzyme plan to report the full data from this study at an upcoming medical meeting.
- We and Akcea published clinical data from two novel lipid drugs, volanesorsen and ISIS-APO(a)$_{Rx}$, in the New England Journal of Medicine and The Lancet, respectively. These data highlight the significant interest from the medical community in our and Akcea's lipid drugs and the medical importance of the clinical data from these programs.
- Volanesorsen was granted orphan drug designation from the FDA for the treatment of patients with familial chylomicronemia syndrome.
- We continued to advance our pipeline of drugs:
  - We and Akcea initiated a Phase 3 study of volanesorsen in patients with familial partial lipodystrophy. This study is designed to support regulatory filing for volanesorsen in this patient population.
  - We initiated a Phase 2 study of ISIS-FXI$_{Rx}$ in patients who have compromised renal function. These data will be important to form the basis for Bayer's first Phase 3 study.
  - We initiated a Phase 2 dose-optimization study of ISIS-GCGR$_{Rx}$ in patients with type 2 diabetes.
  - We initiated a Phase 1/2 study of ISIS-HTT$_{Rx}$ in patients with Huntington's disease (HD). ISIS-HTT$_{Rx}$ was granted orphan drug designation by the European Medicines Agency for the treatment of patients with HD.
  - We initiated a Phase 2 study to evaluate the safety and activity of ISIS-FGFR4$_{Rx}$ in obese patients.
  - We initiated Phase 1 studies of ISIS-DGAT2$_{Rx}$ and ISIS-GSK4-L$_{Rx}$ in healthy volunteers.

Critical Accounting Policies

We prepare our condensed consolidated financial statements in conformity with accounting principles generally accepted in the United States. 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 reviews the development, selection and disclosure of such estimates with our audit committee of our board of directors. In the following paragraphs, we describe the specific risks associated with these critical accounting policies and we caution that future events rarely develop exactly as one may expect, and that best estimates may require adjustment.

The following are our significant accounting policies, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results:

- Assessing the propriety of revenue recognition and associated deferred revenue;
- Determining the proper valuation of investments in marketable securities and other equity investments;
- Determining the appropriate cost estimates for unbilled preclinical studies and clinical development activities; and
- Estimating our net deferred income tax asset valuation allowance.

Based on our ongoing evaluation of our business, in the second quarter of 2015 we determined the following policies are no longer critical to our business and have therefore omitted them from our critical accounting policies:

- Assessing the recoverability of long-lived assets, including property and equipment, intellectual property and licensed technology; and
- Determining the fair value of convertible debt without the conversion feature.

There have been no other material changes to our critical accounting policies and estimates from the information provided in Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations", included in our Annual Report on Form 10-K for the year ended December 31, 2014.

Results of Operations

Revenue

Total revenue for the three and nine months ended September 30, 2015 was $49.1 million and $232.1 million, respectively, compared to $44.1 million and $129.3 million for the same periods in 2014. We earned $180.9 million of revenue from the license fee we received from Bayer and milestone payments we earned from our partners and $49.5 million from the amortization of upfront fees and manufacturing services we performed for our partners during the nine months ended September 30, 2015.

Our revenue fluctuates based on the nature and timing of payments under agreements with our partners and consists primarily of revenue from the amortization of upfront fees, milestone payments and license fees.

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for the three and nine months ended September 30, 2015 was $48.9 million and $230.5 million, respectively, compared to $43.8 million and $120.0 million for the same periods in 2014. Our revenue for the nine months ended September 30, 2015 consisted of the following:

- $91.2 million from Bayer in connection with our exclusive license agreement for ISIS-FXI$_{Rx}$;
- $51.7 million in milestone payments from Biogen for advancing nusinersen in late-stage clinical development, advancing ISIS-BIIB4$_{Rx}$ into development and validating two new undisclosed targets for neurological disorders;
- $22 million from a milestone payment from Roche for initiating a Phase 1/2 study of ISIS-HTT$_{Rx}$;
- $15 million from a milestone payment from GSK for advancing the Phase 3 study of ISIS-TTR$_{Rx}$; and
- $49.5 million from the amortization of upfront fees and manufacturing services we performed for our partners.

Already in the fourth quarter of 2015, we have earned $16 million in milestone payments from Biogen and GSK.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties for the three and nine months ended September 30, 2015 was $0.2 million and $1.7 million, respectively, compared to $0.3 million and $9.3 million for the same periods in 2014. The decrease in 2015 compared to 2014 was primarily a result of the $7.7 million in sublicensing revenue we earned in the first quarter of 2014 from Alnylam related to its license of our technology to one of its partners.

Operating Expenses

Operating expenses for the three and nine months ended September 30, 2015 were $97.3 million and $245.0 million, respectively, and increased compared to $65.6 million and $187.1 million for the same periods in 2014. We are conducting more later-stage clinical trials in 2015 than we did in 2014, including the continuation of our Phase 3 programs for ISIS-TTR_{Rx}, nusinersen, and volanesorsen. As drugs move forward to more advanced stages of development, including into larger, longer clinical studies, the costs of development increase. As our Phase 3 programs continue to progress in the fourth quarter, we expect the costs associated with these programs to continue to increase. Additionally, our operating expenses increased in 2015 as Akcea is building the commercial infrastructure and continues to advance the pre-commercialization activities necessary to successfully launch volanesorsen within the next few years. We also had an increase in stock compensation expense due to the increase in our stock price in January 2015 compared to January 2014.

In 2015 we began disclosing segment information for Akcea, our wholly owned subsidiary. We have revised 2014 for comparative purposes to show operating costs for Akcea-related projects.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2015	2014	2015	2014
Isis Core	$ 72,098	$ 50,831	$ 178,354	$ 148,015
Akcea Therapeutics	13,350	6,607	27,879	16,202
Elimination of intercompany activity	(3,186)	—	(3,186)	—
Total operating expenses, excluding non-cash compensation expense related to equity awards	82,262	57,438	203,047	164,217
Non-cash compensation expense related to equity awards	14,997	8,118	41,907	22,894
Total operating expenses	$ 97,259	$ 65,556	$ 244,954	$ 187,111

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,	
	2015	2014	2015	2014
Research, development and patent expenses	$ 77,211	$ 54,480	$ 188,714	$ 154,919
Non-cash compensation expense related to equity awards	11,297	6,606	32,248	18,879
Total research, development and patent expenses	$ 88,508	$ 61,086	$ 220,962	$ 173,798

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2015	2014	2015	2014
Isis Core	$ 68,269	$ 48,020	$ 167,019	$ 139,210
Akcea Therapeutics	12,128	6,460	24,881	15,709
Elimination of intercompany activity	(3,186)	—	(3,186)	—
Total research, development and patent expenses, excluding non-cash compensation expense related to equity awards	77,211	54,480	188,714	154,919
Non-cash compensation expense related to equity awards	11,297	6,606	32,248	18,879
Total research, development and patent expenses	$ 88,508	$ 61,086	$ 220,962	$ 173,798

For the three and nine months ended September 30, 2015, our total research, development and patent expenses were $77.2 million and $188.7 million, respectively, compared to $54.5 million and $154.9 million for the same periods in 2014, and were higher primarily due to the progression of our drugs currently in Phase 3 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 partners. Antisense drug discovery is also the function that is responsible for advancing our 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) and are part of our Isis Core business segment:

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2015	2014	2015	2014
Antisense drug discovery expenses	$ 12,329	$ 11,151	$ 33,643	$ 31,006
Non-cash compensation expense related to equity awards	3,120	1,829	8,974	5,359
Total antisense drug discovery	$ 15,449	$ 12,980	$ 42,617	$ 36,365

Antisense drug discovery costs for the three and nine months ended September 30, 2015 were $12.3 million and $33.6 million, respectively, and were slightly higher as expected, compared to $11.2 million and $31.0 million for the same periods in 2014. Expenses were higher because we are conducting more research activities to support our partnerships. 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,	
	2015	2014	2015	2014
Nusinersen	$ 11,893	$ 4,956	$ 24,223	$ 12,392
Volanesorsen	5,450	3,318	11,637	6,329
ISIS-TTR$_{Rx}$	4,647	2,623	12,259	7,032
KYNAMRO	715	1,383	3,036	3,800
Other antisense development products	19,810	11,502	39,276	35,193
Development overhead costs	8,678	7,256	25,779	22,837
Total antisense drug development, excluding non-cash compensation expense related to equity awards	51,193	31,038	116,210	87,583
Non-cash compensation expense related to equity awards	4,300	2,536	11,671	6,937
Total antisense drug development	$ 55,493	$ 33,574	$ 127,881	$ 94,520

Antisense drug development expenses were $51.2 million and $116.2 million for the three and nine months ended September 30, 2015, respectively, compared to $31.0 million and $87.6 million for the same periods in 2014. Expenses for the nine months ended September 30, 2015 were higher compared to the same period in 2014 primarily due to the progression of our drugs currently in Phase 3 trials. As drugs move forward to more advanced stages of development, including into larger, longer clinical studies, the costs of development increase. All amounts exclude non-cash compensation expense related to equity awards. In our Form 10-K for fiscal year end 2014, we began presenting salaries and benefits in the development overhead costs line in our antisense drug development table. We have adjusted 2014 to conform to the current year presentation.

Our antisense drug development expenses by segment were as follows (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2015	2014	2015	2014
Isis Core	$ 42,731	$ 25,154	$ 95,929	$ 73,552
Akcea Therapeutics	8,462	5,884	20,281	14,031
Non-cash compensation expense related to equity awards	4,300	2,536	11,671	6,937
Total antisense drug development	$ 55,493	$ 33,574	$ 127,881	$ 94,520

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 may 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 drugs in preclinical and early stage clinical research, the fluctuations in expenses from drug to drug, 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.

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. Our manufacturing and operations function is responsible for providing drug supplies to antisense drug development, our Akcea subsidiary and our collaboration partners. Our manufacturing procedures include testing to satisfy good laboratory and good manufacturing practice requirements.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2015	2014	2015	2014
Manufacturing and operations	$ 6,921	$ 5,562	$ 18,904	$ 16,554
Non-cash compensation expense related to equity awards	1,090	756	3,434	2,205
Total manufacturing and operations	$ 8,011	$ 6,318	$ 22,338	$ 18,759

Manufacturing and operations expenses were $6.9 million and $18.9 million for the three and nine months ended September 30, 2015, respectively, and increased compared to $5.6 million and $16.6 million for the same periods in 2014. The increase in manufacturing and operations expenses was primarily related to the manufacturing activities needed to support the increase in our drug development activities. All amounts exclude non-cash compensation expense related to equity awards.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2015	2014	2015	2014
Isis Core	$ 6,477	$ 5,118	$ 17,917	**$ 15,229**
Akcea Therapeutics	3,630	444	4,173	1,325
Elimination of intercompany activity	(3,186)	—	(3,186)	—
Total manufacturing and operations, excluding non-cash compensation expense related to equity awards	6,921	5,562	18,904	16,554
Non-cash compensation expense related to equity awards	1,090	756	3,434	2,205
Total manufacturing and operations	$ 8,011	$ 6,318	$ 22,338	$ 18,759

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 costs (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2015	2014	2015	2014
Personnel costs	$ 2,379	$ 2,278	$ 7,442	$ 7,226
Occupancy	2,180	1,937	5,900	5,491
Patent expenses	483	882	1,547	1,962
Depreciation and amortization	525	548	1,617	1,697
Insurance	343	305	982	898
Other	858	779	2,469	2,502
Total R&D support costs, excluding non-cash compensation expense related to equity awards	6,768	6,729	19,957	19,776
Non-cash compensation expense related to equity awards	2,787	1,485	8,169	4,378
Total R&D support costs	$ 9,555	$ 8,214	$ 28,126	$ 24,154

R&D support costs for the three and nine months ended September 30, 2015 were $6.8 million and $20.0 million, respectively, compared to $6.7 million and $19.8 million for the same periods in 2014. Expenses were essentially flat compared to the same periods in 2014. All amounts exclude non-cash compensation expense related to equity awards.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2015	2014	2015	2014
Isis Core	$ 6,732	$ 6,597	$ 19,530	$ 19,423
Akcea Therapeutics	36	132	427	353
Non-cash compensation expense related to equity awards	2,787	1,485	8,169	4,378
Total R&D support costs	$ 9,555	$ 8,214	$ 28,126	$ 24,154

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 and utilities costs that we need to support the corporate functions listed above.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2015	2014	2015	2014
General and administrative expenses	$ 5,051	$ 2,958	$ 14,333	$ 9,298
Non-cash compensation expense related to equity awards	3,700	1,512	9,659	4,015
Total general and administrative expenses	$ 8,751	$ 4,470	$ 23,992	$ 13,313

General and administrative expenses were $5.1 million and $14.3 million for the three and nine months ended September 30, 2015, respectively, and increased compared to $3.0 million and $9.3 million for the same periods in 2014 primarily due to increased personnel costs and the addition of Akcea. Expenses for Akcea will increase as it continues to build the commercial infrastructure and advance the pre-commercialization activities necessary for the commercial launch of volanesorsen. All amounts exclude non-cash compensation expense related to equity awards.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2015	2014	2015	2014
Isis Core	$ 3,829	$ 2,811	$ 11,335	$ 8,805
Akcea Therapeutics	1,222	147	2,998	493
Non-cash compensation expense related to equity awards	3,700	1,512	9,659	4,015
Total general and administrative expenses	$ 8,751	$ 4,470	$ 23,992	$ 13,313

Akcea Therapeutics, Inc.

The following table sets forth information on operating expenses (in thousands) for our Akcea Therapeutics business segment:

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2015	2014	2015	2014
Development and patent expenses	$ 12,128	$ 6,460	$ 24,881	$ 15,709
General and administrative expenses	1,222	147	2,998	493
Total operating expenses, excluding non-cash compensation expense related to equity awards	13,350	6,607	27,879	16,202
Non-cash compensation expense related to equity awards	1,271	—	2,782	—
Total Akcea Therapeutics operating expenses	$ 14,621	$ 6,607	$ 30,661	$ 16,202

Expenses for Akcea were $13.4 million and $27.9 million for the three and nine months ended September 30, 2015, respectively, and increased compared to $6.6 million and $16.2 million for the same periods in 2014. The increase in expenses was primarily due to Akcea's Phase 3 program for volanesorsen, which continues to advance, and other projects, including ISIS-APO(a)$_{Rx}$ and ISIS-ANGPTL3$_{Rx}$. Also, starting in 2015, Akcea incurred additional general and administrative costs necessary to operate, including costs to begin building the commercial infrastructure and advance the pre-commercialization activities necessary to successfully launch volanesorsen within the next few years. We expect that these costs will continue to increase in the fourth quarter of 2015. For 2015 and 2014, we allocated a portion of Isis' general and administrative and R&D support costs (included in Development expenses in the table above) to Akcea for work we performed on behalf of Akcea. All amounts exclude non-cash compensation expense related to equity awards.

Investment Income

Investment income for the three and nine months ended September 30, 2015 was $1.2 million and $2.9 million, respectively, compared to $0.7 million and $2.0 million for the same periods in 2014. The increase in investment income was primarily due to a higher average cash balance and an improvement in the market conditions during 2015 compared to 2014.

Interest Expense

Interest expense includes non-cash amortization of the debt discount and debt issuance costs plus interest expense payable in cash for our 1 percent and 2¾ percent notes, non-cash interest expense related to the long-term financing liability for our primary facility and other miscellaneous debt.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2015	2014	2015	2014
2¾ percent notes:				
Non-cash amortization of the debt discount and debt issuance costs	$ 639	$ 1,879	$ 1,877	$ 5,515
Interest expense payable in cash	421	1,384	1,263	4,151
1 percent notes:				
Non-cash amortization of the debt discount and debt issuance costs	5,216	—	15,356	—
Interest expense payable in cash	1,250	—	3,749	—
Non-cash interest expense for long-term financing liability	1,668	1,657	4,994	4,962
Other	39	78	142	275
Total interest expense	$ 9,233	$ 4,998	$ 27,381	$ 14,902

Interest expense for the three and nine months ended September 30, 2015 was $9.2 million and $27.4 million, respectively, compared to $5.0 million and $14.9 million for the same periods in 2014. The increase in interest expense was primarily due to the increase in non-cash amortization of the debt discount and debt issuance costs for our 1 percent notes we issued in November 2014. Additionally, since we had more debt outstanding in 2015, our interest expense payable in cash increased modestly. In November 2014, we completed a $500 million convertible debt offering. The notes mature in 2021 and bear interest at 1 percent. We used a substantial portion of the net proceeds from the issuance of the 1 percent notes to repurchase $140 million in principal of our 2¾ percent convertible notes. The new principal balance of the 2¾ percent notes is $61.2 million. We record non-cash amortization of the debt discount on our convertible notes because we account for our convertible notes by separating the liability and equity components of the instruments in a manner that reflects our nonconvertible debt borrowing rate. As a result, we assigned a value to the debt component of our convertible notes equal to the estimated fair value of similar debt instruments without the conversion feature. This means we recorded our convertible notes at a discount that we are amortizing over the life of the notes as non-cash interest expense.

Gain on Investment in Regulus Therapeutics Inc.

For the three and nine months ended September 30, 2015, we recorded a gain on our investment in Regulus of $20.2 million, compared to a gain of $0.5 million for the three and nine months ended September 30, 2014 related to our sale of a portion of our Regulus common stock.

Net Loss and Net Loss per Share

Net loss for the three and nine months ended September 30, 2015 was $35.8 million and $16.8 million, respectively, compared to $26.7 million and $70.0 million for the same periods in 2014. Basic and diluted net loss per share for the three and nine months ended September 30, 2015 was $0.30 and $0.14, respectively, compared to $0.23 and $0.60 for the same periods in 2014. We had a lower net loss in the first nine months of 2015 primarily due to the revenue we earned from our exclusive license agreement with Bayer for ISIS-FXI$_{Rx}$ in the second quarter of 2015.

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, 2015, we have earned approximately $1.7 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, 2015, we have raised net proceeds of approximately $1.1 billion from the sale of our equity securities and we have borrowed approximately $1.3 billion under long-term debt arrangements to finance a portion of our operations.

At September 30, 2015, we had cash, cash equivalents and short-term investments of $812.2 million and stockholders' equity of $245.4 million. In comparison, we had cash, cash equivalents and short-term investments of $728.8 million and stockholders' equity of $257.8 million at December 31, 2014. At September 30, 2015, we had consolidated working capital of $746.1 million, compared to $721.3 million at December 31, 2014. The increase in our cash and working capital primarily relates to the nearly $300 million we have received from our partners through September 30, 2015.

As of September 30, 2015, our debt and other obligations totaled $641.4 million compared to $643.5 million at December 31, 2014.

The following table summarizes our contractual obligations as of September 30, 2015. 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**
1 percent Notes (principal and interest payable)	$ 532.5	$ 5.0	$ 10.0	$ 10.0	$ 507.5
2¾ percent Notes (principal and interest payable)	$ 68.8	$ 1.7	$ 3.4	$ 63.7	$ —
Facility Rent Payments	$ 127.1	$ 6.5	$ 13.4	$ 14.2	$ 93.0
Equipment Financing Arrangements (principal and interest payable)	$ 0.7	$ 0.7	$ —	$ —	$ —
Other Obligations (principal and interest payable)	$ 1.3	$ 0.1	$ 0.1	$ 0.1	$ 1.0
Operating Leases	$ 24.8	$ 1.9	$ 3.4	$ 3.0	$ 16.5
Total	$ 755.2	$ 15.9	$ 30.3	$ 91.0	$ 618.0

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

Convertible Debt Summary

In November 2014, we completed a $500 million offering of convertible senior notes, which mature in 2021 and bear interest at 1 percent. We used a substantial portion of the net proceeds from the issuance of these notes to repurchase $140 million in principal of our 2¾ percent notes. As a result, the new principal balance of the 2¾ percent notes is $61.2 million.

At September 30, 2015 our outstanding convertible debt was as follows (amounts in millions except price per share data):

	1 Percent Notes	2¾ Percent Notes
Outstanding principal balance	$ 500.0	$ 61.2
Issue date	November 2014	August 2012
Maturity date	November 2021	October 2019
Interest rate	1 percent	2¾ percent
Conversion price per share	$ 66.81	$ 16.63
Total shares of common stock subject to conversion	7.5	3.7

Interest is payable semi-annually for both the 1 percent and 2¾ percent notes. The notes are convertible under certain conditions, at the option of the note holders. We settle conversions of the notes, at our election, in cash, shares of our common stock or a combination of both.

1 Percent Convertible Senior Notes

We may not redeem the 1 percent notes prior to maturity, and no sinking fund is provided for them. Holders of the 1 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 1 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.

2¾ Percent Convertible Senior Notes

We may 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.

Line of Credit Arrangement

In June 2015, we entered into a five-year revolving line of credit agreement with Morgan Stanley Private Bank, National Association, or Morgan Stanley. Under the credit agreement, Morgan Stanley will provide a maximum of $20 million of revolving credit for general working capital purposes. Any loans under the credit agreement have interest payable monthly in arrears at a rate based on our option of:

(i) a floating rate equal to the one-month London Interbank Offered Rate, or LIBOR, in effect plus 1.25 percent per annum;
(ii) a fixed rate equal to LIBOR plus 1.25 percent for a period of one, two, three, four, six, or twelve months as elected by us; or
(iii) a fixed rate equal to the LIBOR swap rate during the period of the loan.

Additionally, we will pay 0.25 percent per annum, payable quarterly in arrears, for any amount unused under the credit facility beginning after June 2016. We did not have any outstanding borrowings under the credit facility as of September 30, 2015.

The credit agreement includes customary affirmative and negative covenants and restrictions. We were in compliance with all covenants of the credit agreement as of September 30, 2015.

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. As of September 30, 2015, our outstanding borrowings under this loan agreement were at a weighted average interest rate of 4.39 percent. The carrying balance under this loan agreement at September 30, 2015 and December 31, 2014 was $0.7 million and $3.2 million, respectively. We will continue to use equipment lease financing as long as the terms remain commercially attractive.

Research and Development Facility Lease Obligation

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 apply our rent payments, which began on January 1, 2012, against the liability over the term of the lease.

In addition to contractual obligations, we had outstanding purchase orders as of September 30, 2015 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, 2014.

Risks Associated with our Isis Core and Akcea Therapeutics Businesses

If the market does not accept KYNAMRO and our other drugs, including volanesorsen, nusinersen and ISIS-TTR$_{Rx}$, 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 are approved for marketing, including volanesorsen, nusinersen and ISIS-TTR$_{Rx}$, 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 prescribe 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, including volanesorsen, nusinersen and ISIS-TTR$_{Rx}$, 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, including volanesorsen, nusinersen and ISIS-TTR$_{Rx}$, unaffordable.

If we fail to compete effectively, our drugs, including KYNAMRO, volanesorsen, nusinersen, and ISIS-TTR$_{Rx}$, will not contribute significant revenues.

Our competitors engage in 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, volanesorsen, nusinersen and ISIS-TTR$_{Rx}$, 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, which is approved, volanesorsen, nusinersen and ISIS-TTR$_{Rx}$.

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 such products. 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 or Akcea 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 could suffer if KYNAMRO cannot compete effectively in the marketplace.

There are several pharmaceutical and biotechnology companies engaged in the development or commercialization of products against targets that are also targets of products in our development pipeline. For example, drugs like tafamadis, diflunisal, and patisiran could compete with ISIS-TTR$_{Rx}$, drugs like Glybera, pradigastat and CAT-2003 could compete with volanesorsen, and RG7800 and olesoxime and the other products that may emerge from early development programs designed to treat patients with SMA could compete with nusinersen.

KYNAMRO is, and, following approval any of our other drugs, including volanesorsen, nusinersen and ISIS-TTR$_{Rx}$, 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. We or our partners may not obtain the labeling claims necessary or desirable for successfully commercializing our drug products, including our approved drug, KYNAMRO, and our drugs in development including: volanesorsen, nusinersen and ISIS-TTR$_{Rx}$.

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, volanesorsen, nusinersen and ISIS-TTR$_{Rx}$.

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 and the long term supply of KYNAMRO drug substance. 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 or initial approvals for volanesorsen, nusinersen and ISIS-TTR$_{Rx}$, we or our partners cannot sell them in the applicable markets.

We cannot guarantee that any of our drugs, including volanesorsen, nusinersen and ISIS-TTR$_{Rx}$, will be safe and effective, or will be approved for commercialization. In addition, we cannot guarantee that KYNAMRO will be approved in additional markets 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, volanesorsen, nusinersen and ISIS-TTR$_{Rx}$, before they 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 or any of our other drugs including, volanesorsen, nusinersen and ISIS-TTR$_{Rx}$ 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, volanesorsen, nusinersen and ISIS-TTR$_{Rx}$, 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 initial approvals for volanesorsen, nusinersen and ISIS-TTR$_{Rx}$, 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.

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, including volanesorsen, nusinersen and ISIS-TTR$_{Rx}$. If any of our drugs in clinical studies, including KYNAMRO, volanesorsen, nusinersen and ISIS-TTR$_{Rx}$, do 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 and the Phase 3 studies for volanesorsen, nusinersen and ISIS-TTR$_{Rx}$. 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 and the Phase 3 studies for volanesorsen, nusinersen and ISIS-TTR$_{Rx}$, 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 additional approvals for KYNAMRO, and initial approvals for volanesorsen, nusinersen and ISIS-TTR$_{Rx}$, or result in enforcement action after approval that could limit the commercial success of our drugs, including KYNAMRO, volanesorsen, nusinersen and ISIS-TTR$_{Rx}$.

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, we use clinical research organizations, such as Icon Clinical Research Limited, INC Research Toronto, Inc. and Medpace for the clinical studies for our drugs, including KYNAMRO, volanesorsen, nusinersen and ISIS-TTR$_{Rx}$. 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 and initial approvals for volanesorsen, nusinersen and ISIS-TTR$_{Rx}$.

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, 2015, we had an accumulated deficit of approximately $1.0 billion and stockholders' equity of approximately $245.4 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. 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, Bayer, Biogen, Genzyme, GSK, and Roche these collaborations may not continue or result in commercialized drugs, or may not progress as quickly as we first anticipated.

For example, a collaborator such as AstraZeneca, Bayer, Biogen, Genzyme, GSK, or Roche, 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, volanesorsen, nusinersen and ISIS-TTR_{Rx}.

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 or milestones related to the Phase 3 programs for volanesorsen, nusinersen and ISIS-TTR_{Rx}, the price of our securities could decrease.

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.

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 November 2013 we filed a patent infringement lawsuit against Gilead Sciences Inc. in the United States District Court of the Northern District of California. Intellectual property lawsuits 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.

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, 2015, we had cash, cash equivalents and short-term investments equal to $812.2 million. If we do not meet our goals to successfully commercialize KYNAMRO and our other drugs, including volanesorsen, nusinersen and ISIS-TTR_{Rx}, 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:

- 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, including volanesorsen, nusinersen and ISIS-TTR_{Rx}.

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, 2015, the market price of our common stock ranged from $35.26 to $77.80 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, changes in payors' reimbursement policies, 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.

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.

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 shutdown 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.

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 11.2 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 in the past experienced periods 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. It is possible that a crisis in the global credit markets, the U.S. capital markets, the financial services industry or 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.

ITEM 4. CONTROLS AND PROCEDURES

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.

As of our most recently completed fiscal year and as of the end of the period covered by this Quarterly Report on Form 10-Q, we carried out an evaluation 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, under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. Based on our evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of September 30, 2015. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to September 30, 2015.

We also performed an evaluation 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. We conducted this evaluation under the supervision of and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. 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.

PART II — OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

Gilead Litigation

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 any valid claim of the named patents and that the patents are not valid. We and Merck Sharp & Dohme Corp. filed our answer denying Gilead's noninfringement and invalidity contentions, contending that Gilead's commercial sale and offer for sale of sofosbuvir prior to the expiration of the '499 and '712 patents will infringe those patents, and requesting monetary damages to compensate for such infringement. Under our agreement with Merck, Merck is responsible for the costs of this suit.

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

Not applicable.

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

ITEM 5. OTHER INFORMATION

Not Applicable.

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.1	Strategic Collaboration Agreement between the Registrant and AstraZeneca AB dated July 31, 2015. Portions of this exhibit have been omitted and separately filed with the SEC.
10.2	Amendment #6 to Research, Development and License Agreement between the Registrant, Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development Limited dated September 2, 2015. Portions of this exhibit have been omitted and separately filed with the SEC.
10.3	Amendment Number One to the Second Amended and Restated Strategic Collaboration and License Agreement between the Registrant and Alnylam Pharmaceuticals, Inc. dated July 13, 2015. Portions of this exhibit have been omitted and separately filed with the SEC.
10.4	Form of Option Agreement for Options granted after September 30, 2015 under the 2011 Equity Incentive Plan.
10.5	Form of Option Agreement for Options granted after September 30, 2015 under the 1989 Stock Option Plan.
31.1	Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification by Chief Financial Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101	The following financial statements from the Isis Pharmaceuticals, Inc. Quarterly Report on Form 10-Q for the quarter ended September 30, 2015, formatted in Extensive Business Reporting Language (XBRL): (i) condensed consolidated balance sheets, (ii) condensed consolidated statements of operations, (iii) condensed consolidated statements of comprehensive loss, (iv) condensed consolidated statements of cash flows and (v) notes to condensed consolidated financial statements (detail tagged).

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 9, 2015
/s/ Elizabeth L. Hougen Elizabeth L. Hougen	Senior Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	November 9, 2015

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

Exhibit 10.1

STRATEGIC COLLABORATION AGREEMENT

BETWEEN

ISIS PHARMACEUTICALS, INC.,

AND

ASTRAZENECA AB

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STRATEGIC COLLABORATION AGREEMENT

This STRATEGIC COLLABORATION AGREEMENT (the "***Agreement***") is entered into as of the 31st day of July, 2015 (the "***Execution 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 with its registered office at SE-151 85 Södertälje, Sweden ("***AstraZeneca***"). AstraZeneca 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, exhibits 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, AstraZeneca 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 Metabolic Disorders ([***]), Cardiovascular Diseases, Kidney Diseases [***] (collectively, the "***Primary Diseases***") and to create antisense drugs to such targets;

WHEREAS, AstraZeneca and Isis desire to enter into a new strategic collaboration in the Primary Diseases to include (i) a core technology research program focused on growing the Parties' collective knowledge on ASO interactions in tissues and cell types relevant to Primary Diseases, (ii) a disease research program focused on the identification, validation, and applications of novel targets to treat the Primary Diseases, and (iii) a drug discovery program focused on [***] and up to [***] additional Collaboration Targets that have met certain Target Sanction success criteria;

WHEREAS, with regard to the targets selected as Collaboration Targets for development using an ASO, AstraZeneca desires Isis to (i) identify a Lead Candidate for the JSC to consider designating as a Development Candidate (and for AstraZeneca to consider designating as a Candidate Drug) for each of the Collaboration Targets, and (ii) with respect to Collaboration Targets that are not [***], provide AstraZeneca an exclusive right to obtain an exclusive license under this Agreement to Research, Develop, Manufacture and Commercialize Products in the Field;

WHEREAS, Isis desires to grant to AstraZeneca and AstraZeneca desires to accept from Isis as of the Effective Date an exclusive license to Research, Develop, Manufacture and Commercialize [***] Products;

WHEREAS, Isis also desires to grant to AstraZeneca and AstraZeneca desires to accept from Isis a non-exclusive license under program technology made by Isis under this Agreement and any of Isis' background technology necessary to practice such program technology for AstraZeneca to use in certain fields; and

WHEREAS, Isis and AstraZeneca have other on-going agreements, including the Collaboration, License and Development Agreement effective as of 7 December 2012 (as amended) and the Research Collaboration and License Agreement effective as of 15 October 2014. The strategic collaboration set forth in this Agreement is independent from such other agreements.

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

ARTICLE 1.
RESEARCH COLLABORATION; RIGHT TO OBTAIN EXCLUSIVE LICENSES

1.1. Research Collaboration Overview.

1.1.1. The intent of the Research Collaboration is for the Parties to conduct (1) a core technology research program focused on growing the Parties' collective knowledge on systemic delivery of ASO interactions in tissues and cell types relevant to Primary Diseases, (2) a disease research program focused on the identification, validation, and applications of certain novel Targets to treat the Primary Diseases, and (3) a drug discovery program focused on Targets that meet certain Target Sanction success criteria in the disease research program.

1.1.2. At the beginning and throughout the term of the disease research program, the Parties (including through the JSC) will collaboratively discuss and identify Targets that the Parties are potentially interested in pursuing in the disease research program to treat the Primary Diseases. When Targets of interest are identified, the JSC will determine which Targets are eligible for inclusion in the disease research program. AstraZeneca may either add such Eligible Targets directly to the High Interest Target List to commence the work necessary to validate such Targets, or hold a limited number of such Eligible Targets in reserve for a period of time (before deciding whether to add such Targets to the High Interest Target List).

1.1.3. Isis, and in some cases together with AstraZeneca, will perform Target validation activities under the disease research program on Eligible Targets that the JSC (or AstraZeneca) has added to the list of High Interest Targets. Once a High Interest Target reaches Target Sanction, the JSC may select such Target to be the subject of a Collaboration Program under this Agreement.

1.1.4. For each Collaboration Program, Isis will use Commercially Reasonable Efforts to conduct drug discovery activities and generate [***] Lead Candidate for the JSC to consider designating as a Development Candidate.

1.1.5. For each Collaboration Program that is not the [***] Program, on a Collaboration Target-by-Collaboration Target basis, after the JSC or AstraZeneca determines that a Lead Compound has met the success criteria and such Lead Compound is designated a Development Candidate, AstraZeneca will have the right to obtain an exclusive license to further Research, Develop, Manufacture and ultimately Commercialize such Development Candidate (and any other Compounds designed to bind to such Collaboration Target).

1.1.6. [***] is a Collaboration Target (and will be deemed to have been so designated by the JSC on the Effective Date) and the drug discovery program for [***] will be the first Collaboration Program under this Agreement. AstraZeneca has an exclusive license from Isis to further Research, Develop, Manufacture and ultimately Commercialize [***] Compounds.

1.1.7. 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 with respect to the Research Collaboration, 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, Isis and AstraZeneca will conduct two research programs, each under a separate mutually agreed plan. The data generated from these two research programs will inform the Drug Discovery Programs.

1.2.1. ***Core Research Program***. The core research program will cover research focused on growing the Parties' collective knowledge of systemic delivery of ASO interactions in tissues and cell types relevant to Primary Diseases (such program, the "***Core Research Program***" and the plan for such program, the "***Core Research Plan***"). The Parties will base the Core Research Plan on the preliminary plan attached at SCHEDULE 1.2.1.

1.2.2. ***Disease Research Program***. The disease research program will focus on the identification and validation of High Interest Targets that may be designated as Collaboration Targets (such program, the "***Disease Research Program***" and the plan for such program, the "***Disease Research Plan***"). The Disease Research Plan will include at a minimum, the items set forth on SCHEDULE 1.2.2 and on approval by the JSC will be attached to the JSC minutes. AstraZeneca may, [***], supplement Isis' efforts in the Disease Research Program with AstraZeneca's own scientists at various points throughout the Disease Research Term.

1.2.3. ***Updating the Research Plans***. The Core Research Plan (based on the preliminary plan attached at SCHEDULE 1.2.1) and the Disease Research Plan will be mutually agreed to by the JSC within [***] after the Effective Date and on approval by the JSC will be attached to the JSC minutes. Thereafter, the Parties will update such plans, as needed, and the updated plans will be reviewed and approved by the JSC at least [***] before the beginning of each Calendar Year (to facilitate each Party's budgeting). The first update to the Disease Research Plan will occur after the first High Interest Target is selected. Each update to the Disease Research Plan will include, at a minimum (i) the High Interest Targets to be worked on in the Disease Research Plan in each Calendar Year (or remaining portion thereof) and, if not already commenced, the date on which the JSC anticipates that work on each High Interest Target will commence; and (ii) the activities to support Target Sanction for any High Interest Target included in the Disease Research Plan (including any work on High Interest Targets that is ongoing).

1.2.4. ***Feasibility***. Neither Party will be required to complete any activities under the Core Research Plan or the 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.

1.3. **Core Research Term; Disease Research Term**.

1.3.1. ***Core Research Term***. The term for the conduct of the Core Research Program will begin on the Effective Date and will end on the [***] anniversary of the Effective Date (the "***Core Research Term***").

1.3.2. ***Disease Research Term***. The term for the conduct of the Disease Research Program will begin on the Effective Date and will end on the [***] anniversary of the Effective Date (the "***Disease Research Term***"); *provided, however*, if, by the [***] anniversary of the Effective Date Isis has not completed the activities set forth in the Disease Research Plan to support Target Sanction for [***] High Interest Targets, [***].

1.4. **Collaborative Process to Identify Potentially Eligible Targets – Overview**. Throughout the Disease Research Term, including at the first meeting of the JSC, the Parties will collaboratively discuss and identify Targets that the Parties are potentially interested in pursuing in the Disease Research Program to treat the Primary Diseases. For all of the potential Targets identified through this collaborative process, using the steps identified in Sections 1.5 through 1.7 below, the JSC will first determine whether the Targets being considered are eligible for possible inclusion in the Disease Research Plan, and AstraZeneca may designate Eligible Targets that are of interest to AstraZeneca as High Interest Targets for which activities to support Target Sanction will be conducted, or may choose to hold a limited number of such Eligible Targets in reserve (before deciding whether to add such Targets to the High Interest Target List).

1.5. **Eligible Targets**. AstraZeneca (through the JSC) may consider for designation as High Interest Targets any Targets that are not excluded by any of the Exclusion Criteria (as set forth in Section 1.6.1) (each, an "***Eligible Target***"). The various sources for potential Eligible Targets that may be designated as High Interest Targets include [***]. An Eligible Target may have as its primary disease association a disease that is not a Primary Disease but the focus of each Disease Research Plan will be the Primary Diseases. [***]. To that end, at each JSC meeting, Isis will review with AstraZeneca [***]. Isis' obligations under this paragraph will end on the earlier of (i) [***], and (ii) [***].

1.6. Exclusion Criteria.

1.6.1. List of Exclusion Criteria to Consider for Proposed Targets. If a Target proposed to be designated as a Reserved Target or High Interest Target meets any of the following criteria listed in items (a) through (g) (such criteria listed in items (a) through (g), the "***Exclusion Criteria***"), such Target is not an Eligible Target and will not be added to the Reserved Target List or the High Interest Target List:

[***];

provided, that [***].

1.6.2. Notice of Any Applicable Exclusion Criteria. Isis will (through the JSC) notify AstraZeneca if any of the Exclusion Criteria apply to a Target AstraZeneca requests for consideration as a Reserved Target or High Interest Target ([***]), and shall provide such information as is reasonably necessary to allow the JSC to discuss and verify such conclusion; *provided that* [***]. Upon requesting that a Target be considered as a Reserved Target or a Target that is not a Reserved Target be considered a High Interest Target, AstraZeneca will also notify Isis in writing if AstraZeneca has an internal program (regardless of therapeutic modality) for such Target (or protein product thereof).

1.7. High Interest Target List; Reserved Target List. With respect to any Eligible Target, AstraZeneca may either add the Eligible Target directly to the High Interest Target list as described under Section 1.7.1, or hold a limited number of such Eligible Targets in reserve on the Reserved Target List for a period of time as further described in Section 1.7.2 while AstraZeneca considers whether to designate such Eligible Target a High Interest Target.

1.7.1. High Interest Targets.

(a) ***High Interest Target List***. Under the Disease Research Plan, the JSC will establish a prioritized list of Eligible Targets to form the basis for the Disease Research Program (each such Target, a "***High Interest Target***" and such list the "***High Interest Target List***"). The JSC will regularly discuss the Eligible Targets the JSC believes may be designated as High Interest Targets, and will establish criteria and a process for selection and prioritization of High Interest Targets, which may include [***]. During the Disease Research Term, an Eligible Target may be included on the High Interest Target List at any time and such inclusion is separate from the decision to commence work on such High Interest Target under the Disease Research Plan.

(b) ***Schedule for Populating the High Interest Target List.*** Given the time needed to research each High Interest Target, the Parties intend that the JSC will name at least [***] High Interest Targets within the [***] of the Disease Research Term, and at least [***] additional High Interest Targets during each consecutive [***] period thereafter during the Disease Research Term; *provided*, the number of High Interest Targets cannot exceed [***]. Each Party may propose updates, if any, to the High Interest Target List at each meeting of the JSC.

(c) ***Substituting or Removing High Interest Targets***. Prior to [***] for a High Interest Target, the JSC may add a new Eligible Target to the High Interest Target List in substitution for such a Target. In addition, if a High Interest Target is invalidated (e.g., published scientific literature demonstrates the invalidity of the High Interest Target) prior to [***] for such Target, as determined by the JSC, then the JSC will replace such invalidated High Interest Target on the High Interest Target List with another Eligible Target selected by the JSC.

1.7.2. **Reserved Targets**.

(a) ***Reserved Target List***. Under the Disease Research Plan, if the JSC (or AstraZeneca) determines that certain Eligible Targets should be held in reserve for consideration as potential High Interest Targets, the JSC will establish and maintain in the JSC minutes such a list of Eligible Targets (the "***Reserved Target List***," and each such listed Eligible Target, a "***Reserved Target***"). AstraZeneca may add Eligible Targets to such list at any time during the Disease Research Term. No Eligible Target can be added to the Reserved Target List if by virtue of such addition the number of Eligible Targets on the Reserved Target List will exceed [***] the number of open High Interest Target slots remaining on the High Interest Target List at any given time. The Reserved Target List will include the date that each such Reserved Target was added to the Reserved Target List and each Reserved Target will be automatically removed from the Reserved Target List (and will no longer be a Reserved Target) [***] after it was put on such list. If, at any time, the number of Targets on the Reserved Target List exceeds the maximum number of allowed Reserved Targets by virtue of a decrease in the number of open slots remaining on the High Interest Target List, no Targets will be required to be removed from the Reserved Target List, except by virtue of the passage of time. AstraZeneca will be precluded from adding any additional Eligible Targets to the Reserved Target List if by virtue of such addition it would increase the size of the Reserved Target List above the maximum permitted number of Reserved Targets.

(b) ***Re-designation as a Reserved Target***. Subject to Section 1.7.2(a) with respect to the maximum number of Reserved Targets, the JSC may add a previously removed Target to the Reserved Target List if such Target is still an Eligible Target, and either (i) the data has changed materially on such Target based on either laboratory work or new information discovered in the literature; or (ii) [***] have passed from the time such Target was removed from the Reserved Target List. On such addition, the Eligible Target shall once again be a Reserved Target until automatically removed from the Reserved Target List in accordance with Section 1.7.2(a).

(c) ***Restrictions on Reserved Targets***. During the Disease Research Term until [***] High Interest Targets have been selected to be included on the High Interest Target List, Isis will not and will ensure that its Affiliates will not offer a Reserved Target to a Third Party or grant to any such Third Party any rights to such Reserved Target or any ASOs designed to bind to such Reserved Target so long as such Target remains a Reserved Target.

(d) ***Dissolution of Reserved Target List***. Once substantial activities are initiated under the Disease Research Plan on [***] High Interest Targets, no additional Targets may be added or substituted on the High Interest Target List, and the Reserved Target List will be dissolved. Isis' obligations and AstraZeneca's rights under this Agreement with respect to any Eligible Targets that were on the Reserved Target List at such dissolution will terminate.

1.8. Activities to Support Target Sanction under the Disease Research Program.

(a) Isis will prepare the Disease Research Plan and any updates to such plan (which will include Target Sanction criteria for each High Interest Target), and the JSC will agree on the Disease Research Plan. AstraZeneca will provide input on the Disease Research Plan through the JSC. The criteria to be met and the activities to be conducted for any High Interest Target to achieve Target Sanction will include the criteria and activities set forth on SCHEDULE 1.8.

(b) The JSC will determine the number of High Interest Targets for which activities to support Target Sanction will be conducted during each Calendar Year (or portion thereof for the initial and final periods) of the Disease Research Term, which number will be approximately [***] High Interest Targets during the first whole Calendar Year of the Disease Research Term, and [***] High Interest Targets per Calendar Year during the remainder of the Disease Research Term for a total of [***] High Interest Targets; *provided, however*, that (i) with the JSC's approval Isis may conduct such activities to support Target Sanction on more High Interest Targets per Calendar Year than was otherwise planned hereunder if Isis identifies that certain High Interest Targets require less work to achieve Target Sanction, and (ii) so long as by the end of the Disease Research Term Isis has conducted activities to support Target Sanction for [***] High Interest Targets, Isis may conduct activities to support Target Sanction on fewer High Interest Targets per Calendar Year than was otherwise planned hereunder if one or more High Interest Targets require an unusually large amount of work ([***]).

(c) The Disease Research Plan will identify which Party will be responsible for each of the activities related to such Targets. In accordance with the Disease Research Plan, Isis will use Commercially Reasonable Efforts to perform the Isis Conducted Activities designated under such plan in accordance with the timelines specified therein. If the JSC agrees that AstraZeneca will conduct activities under the Disease Research Plan to supplement Isis' efforts to achieve Target Sanction, then the JSC will update the Disease Research Plan accordingly and AstraZeneca will use Commercially Reasonable Efforts to conduct such AstraZeneca Conducted Activities designated under the Disease Research Plan in accordance with the timelines specified therein. Each Party will be responsible for the cost of the work it conducts under the Disease Research Program. Unless otherwise mutually agreed by the JSC, neither Party will be required to conduct work using [***] that are not similar in cost or technical feasibility to the models such Party uses for its other programs.

1.9. **Targets that are Outside of the Collaboration**. During the Disease Research Term, either Party may work outside of the Research Collaboration on any Target (or the protein product thereof) that is not (i) a Reserved Target, (ii) a High Interest Target, or (iii) a Collaboration Target.

1.10. **Process for Designating High Interest Targets as Collaboration Targets**.

1.10.1. **Review of Target Sanction Data Package**. Upon completion of the activities in the Disease Research Plan to support Target Sanction for a particular High Interest Target, Isis will deliver a Target Sanction Data Package for such High Interest Target to the JSC for review as soon as reasonably practicable for the JSC to determine whether or not such High Interest Target has achieved Target Sanction and thus is eligible to become a Collaboration Target. Each time Isis delivers to the JSC a Target Sanction Data Package for a High Interest Target under this Section 1.10 the Parties will schedule a meeting of the JSC to occur within [***] following delivery of such Target Sanction Data Package. At such meeting (if possible), or within [***] after such meeting, the JSC (or, if the JSC cannot agree, AstraZeneca) will determine and record in the JSC minutes whether such High Interest Target has achieved Target Sanction. If the JSC (or, if the JSC cannot agree, AstraZeneca), determines that such High Interest Target has achieved Target Sanction, and AstraZeneca designates such High Interest Target a Collaboration Target, then Isis will promptly commence a Collaboration Program for such Collaboration Target under Section 1.13 below.

1.10.2. **Additional Work to Achieve Target Sanction**. If the JSC determines that such High Interest Target has not achieved Target Sanction status, then the JSC will decide whether or not to revise the Target Sanction criteria and/or determine whether additional work will be conducted for such High Interest Target to achieve Target Sanction (and will update the Disease Research Plan accordingly). The allocation of the expense of and budget for any such additional work and the Party best positioned to conduct such work will be discussed and agreed by the JSC, and [***]. The [***] costs of any such additional work incurred by Isis ([***]) will be billed to AstraZeneca ([***]) and will be invoiced to AstraZeneca on a Calendar Quarter basis and paid by AstraZeneca within [***] of AstraZeneca's receipt of such invoice if and to the extent such invoiced costs are within the budget approved by the JSC for such activities. On conclusion of any additional work Isis shall provide the revised data package to the JSC and Section 1.10.1 shall apply.

1.10.3. **Failure to Achieve Target Sanction.** On a High Interest Target-by-High Interest Target basis, if, on first completion of the activities in the Disease Research Plan to support Target Sanction or, if the JSC agrees that further work will be undertaken with respect to such Target, following completion of any agreed additional work, the JSC (or, if the JSC cannot agree, AstraZeneca) determines that a High Interest Target has not achieved Target Sanction, then on the date of such determination (the "***Target Failure Date***"):

(a) such High Interest Target will not be designated a Collaboration Target and will no longer be a High Interest Target under this Agreement, but will still count against the maximum limit of [***] High Interest Targets under this Agreement;

(b) if and when AstraZeneca timely delivers a Release Notice to Isis, AstraZeneca will be free to Exploit ASOs designed to bind to such former High Interest Target. If AstraZeneca does not timely deliver a Release Notice to Isis, then for a period of [***] from the Target Failure Date, AstraZeneca and its Affiliates will not Exploit ASOs designed to bind to such former High Interest Target other than as research tools in connection with its internal programs; and

(c) Isis will be free to Exploit ASOs designed to bind to such former High Interest Target, *provided, however*, that if AstraZeneca does not timely deliver a Release Notice to Isis, for a period of [***] after the Target Failure Date, (x) any work Isis conducts on such former High Interest Target will be undertaken by Isis for itself and not in collaboration with any Third Party partner (other than Isis' subcontractors acting for or on behalf of Isis or Isis' academic collaborators), and (y) if such former High Interest Target achieves Target Sanction (which shall be deemed to have occurred if [***] with respect to such former High Interest Target) within such [***] period, then Isis will provide written notice to AstraZeneca when it [***]. If, within [***] following receipt of such notice, AstraZeneca delivers written notice to Isis that AstraZeneca desires such former High Interest Target to be restored to this Agreement and designated as a Collaboration Target and agrees to reimburse Isis within [***] for [***] ([***]) incurred by Isis to achieve Target Sanction for such Target after the Target Failure Date through the date Isis delivers such notice that Isis initiated drug discovery activities, then such Target will be a Collaboration Target hereunder and Isis will promptly commence drug discovery work on such Collaboration Target under Section 1.13 below.

(d) without limiting Section 4.4.2, Isis will have exclusive rights (and AstraZeneca will, and hereby does grant Isis an exclusive license) to all data, results and information generated with respect to such former High Interest Target to research, develop, manufacture and commercialize ASOs to such High Interest Target and AstraZeneca will promptly transfer to Isis copies of all such data, results and information in AstraZeneca's possession generated under the Disease Research Program.

1.10.4. **JSC Timing**. The process set forth in this Section 1.10 for the JSC (or, if the JSC cannot agree, AstraZeneca) to make a determination regarding whether a High Interest Target has achieved Target Sanction status, whether such High Interest Target is designated a Collaboration Target, whether the Target Sanction criteria will be revised, and/or whether additional work will be conducted for such High Interest Target to achieve Target Sanction, will in no event exceed [***] after the date the JSC first meets to discuss the Target Sanction Data Package or, if the JSC agrees that additional work should be undertaken, the revised Target Sanction Data Package.

1.11. **End of Core Research Term**. At the end of the Core Research Term, (i) neither Isis nor AstraZeneca will have an obligation to perform any activities under the Core Research Program; and (ii) each Party will promptly transfer to the other (to the extent not previously provided) copies of all data, results and information that it has generated under the Core Research Program and each Party shall be entitled to non-exclusively use and disclose such data, results and information in accordance with Section 4.4.

1.12. **End of the Disease Research Term**. At the end of the Disease Research Term, (i) neither Isis nor AstraZeneca will have an obligation to perform any activities under the Disease Research Program; (ii) the High Interest Target List will be dissolved, (iii) Isis will deliver to AstraZeneca a Target Sanction Data Package (completed to the extent possible with the [***] generated prior to expiration of the Disease Research Term) for any High Interest Target that has not yet achieved Target Sanction and the JSC will consider whether any such High Interest Target has achieved Target Sanction, and AstraZeneca may designate such High Interest Target as a Collaboration Target by delivering a written notice to Isis of such designation within [***] after AstraZeneca's receipt of such Target Sanction Data Package, and (iv) the JSC will be deemed to have determined that any High Interest Targets that have not been designated as Collaboration Targets by such expiry (or by the end of such [***] period), have not achieved Target Sanction and Section 1.10.3 shall apply to each such Target. For clarity, the expiration of the Disease Research Term will not affect AstraZeneca's rights or Isis' obligations with respect to Collaboration Programs under this Agreement, including, in the case of Collaboration Programs, Isis' obligation under Section 1.13.1 to use Commercially Reasonable Efforts to identify a Lead Candidate for each applicable Collaboration Program that satisfies the Development Candidate Success Criteria.

1.13. **Collaboration Program Activities and Term**.

1.13.1. **Drug Discovery Plans**.

(a) An initial draft Drug Discovery Plan for [***] is attached to this Agreement at SCHEDULE 1.13.1(a). For each additional Collaboration Program, within [***] after the designation of the applicable Collaboration Target, Isis will provide the JSC an initial draft drug discovery plan for the applicable Collaboration Target. Each such draft plan will detail the drug discovery activities to identify a Development Candidate under the applicable Collaboration Program and on approval by the JSC will be attached to the JSC minutes (each such plan, a "***Drug Discovery Plan***"). Each Drug Discovery Plan will include the success criteria and the activities that will be performed to achieve Development Candidate designation as set forth in SCHEDULE 1.13.1(b), and will be consistent with the scope and timeframe Isis uses for other similar Isis programs.

(b) AstraZeneca will provide input on each Drug Discovery Plan including any additional success criteria for the Development Candidate that AstraZeneca would like to propose for the JSC's consideration; *provided that*, in any event, each Drug Discovery Plan will include project transition criteria consistent with the internal Isis criteria and, to the extent applicable to ASOs and consistent with the scope of Isis' standard drug discovery activities, Isis will endeavor to conduct the Isis Conducted Activities under each Drug Discovery Plan consistent with the AstraZeneca 5R Framework as notified to Isis from time to time (such framework to be consistent with the framework AstraZeneca uses for other drugs in the applicable AstraZeneca franchise). The current version of the AstraZeneca 5R Framework is attached as EXHIBIT 1. The JSC will review such plan and agree on a final Drug Discovery Plan for each Collaboration Program.

(c) The JSC will review, update and approve the [***] Drug Discovery Plan and Isis will initiate the [***] Drug Discovery Plan as soon as practicable but not later than [***] following the Effective Date. Isis estimates the Isis Conducted Activities under the [***] Drug Discovery Plan will be completed within [***] after such activities are initiated.

(d) Isis will use Commercially Reasonable Efforts to carry out its drug discovery activities for each Collaboration Program pursuant to the applicable Drug Discovery Plan in accordance with the timelines specified therein in a manner consistent with its internal practices for other Targets with the goal of identifying a Development Candidate for the applicable Collaboration Program as soon as practicable. Isis will update each Drug Discovery Plan as needed and submit it to the JSC for its review and approval.

(e) If the JSC agrees that AstraZeneca will conduct any activities under a particular Drug Discovery Plan, then the Parties will update such Drug Discovery Plan accordingly for approval by the JSC and, following such approval, AstraZeneca will use Commercially Reasonable Efforts to conduct such AstraZeneca Conducted Activities designated under such Drug Discovery Plan in accordance with the timelines specified therein [***].

(f) If the JSC or the Parties cannot mutually agree on a final Drug Discovery Plan for a given Collaboration Program, such matter will be resolved by the Senior Representatives in accordance with Section 12.1.1.

1.13.2. **Third Party Obligations Applicable to the Compounds**. While the Parties are reviewing technology options to be used under a Drug Discovery Plan for a potential Development Candidate, the Parties will discuss any existing or potential Third Party Obligations they believe apply or may apply to such technology. Isis will disclose to AstraZeneca any such existing or potential Third Party Obligations known by Isis that apply to technology under consideration by the Parties and Isis will identify which technology is (i) [***] (such [***], the "***New Third Party Compound Technology***") and subject to either (A) an Isis In-License Agreement in existence at such time or (B) an agreement that Isis anticipates will be entered into by Isis and such Third Party (and Section 6.9.2 will apply to any such agreement), (ii) subject to a Prior Agreement, or (iii) otherwise subject to an Isis In-License Agreement. Where AstraZeneca agrees to incorporate technology subject to an Isis In-License Agreement into an ASO under the Drug Discovery Plan, AstraZeneca will pay [***]. On such agreement, Isis will update APPENDIX 3 to include any such in-license agreement.

1.13.3. **Collaboration Program Term**. The period during which the Parties will conduct the Collaboration Programs under Drug Discovery Plans (such period, the "***Collaboration Program Term***") will begin on the Effective Date and will end on the [***] anniversary of the Effective Date; *provided that* (a) if the Disease Research Term is extended under Section 1.3.2 and there are uncompleted activities to be performed for a Collaboration Program under a Drug Discovery Plan under this Section 1.13, then, in order to provide sufficient time to perform such additional activities with respect to such Collaboration Program(s), the Collaboration Program Term for all uncompleted Collaboration Programs will be extended to end on the [***] anniversary of the Effective Date; and (b) if a Target is restored to the collaboration in accordance with Section 1.10.3, then the provisions in this Agreement that were operative during the Collaboration Program Term will apply solely with respect to such Target for such period as is necessary to enable the activities specified in the Drug Discovery Plan for such Target to be performed.

1.14. **Process for Designating Development Candidates**.

1.14.1. **Review of Lead Candidate Data Package.** After the activities set forth in the applicable Drug Discovery Plan are completed for a particular Collaboration Program, Isis will deliver to the JSC the applicable Lead Candidate Data Package for review by the JSC as soon as reasonably practicable for the JSC to determine whether or not the Lead Candidate has met the applicable Development Candidate Success Criteria and whether the JSC (or AstraZeneca) wishes to designate a Development Candidate. Each time Isis delivers to the JSC a Lead Candidate Data Package for a Collaboration Program under this Section 1.14 the Parties will schedule a meeting of the JSC to occur within [***] following delivery of such Lead Candidate Data Package. At such meeting (if possible), or within [***] after such meeting, the JSC (or, if the JSC cannot agree, AstraZeneca) will determine and record in the JSC minutes the determination whether such Lead Candidate has met the applicable Development Candidate Success Criteria. If the JSC (or, if the JSC cannot agree, AstraZeneca) determines such Lead Candidate (or any other Compound included in the Lead Candidate Data Package (the "***Other Leads***," and together with the Lead Candidate, the "***Lead Compounds***")) met such criteria and designates a Lead Compound as a Development Candidate, then AstraZeneca will have the right to undertake the evaluation pursuant to Section 1.16.2 to determine whether AstraZeneca wishes to designate such Development Candidate as a Candidate Drug and (i) obtain an exclusive license from Isis to the Compounds from the applicable Collaboration Program in accordance with Section 1.16 below, or (ii) with respect to [***], maintain the exclusive license to [***] Products in accordance with Section 1.16. If Isis believes that a [***] Compound identified in the Lead Candidate Data Package satisfies the [***] Success Criteria, but the JSC fails to designate such [***] Compound a Development Candidate, the matter shall be resolved in accordance with Section 12.1.1 and if applicable Section 12.1.3.

1.14.2. **Additional Work to Achieve Development Candidate Status**. If with respect to a Collaboration Program, the JSC determines that none of the Lead Compounds has met all the applicable Development Candidate Success Criteria, then the JSC will decide whether or not to revise such success criteria (and designate a Development Candidate based on such revised criteria) and/or determine whether additional work will be conducted for one or more Lead Compounds to meet the Development Candidate Success Criteria (and will update the Drug Discovery Plan accordingly). The allocation of the expense of and budget for any such additional work and the Party best positioned to conduct such work will be discussed and agreed by the JSC, and [***]. The [***] costs of any such additional work incurred by Isis ([***]) will be billed to AstraZeneca ([***]) and will be invoiced to AstraZeneca on a Calendar Quarter basis and paid by AstraZeneca within [***] of AstraZeneca's receipt of such invoice. On conclusion of any additional work Isis shall provide the revised data package to the JSC and Section 1.14.1 shall apply.

1.14.3. **Failure to Achieve Development Candidate Status**. On a Collaboration Target-by-Collaboration Target basis, if, following completion of the activities set forth in the applicable Drug Discovery Plan, the JSC (or, if the JSC cannot agree, AstraZeneca or with respect to [***], unless otherwise agreed by the Parties, the Expert in accordance with Section 12.1.3) determines that none of the Lead Compounds have met the applicable Development Candidate Success Criteria, and the JSC determines that such success criteria will not be revised and that no additional work will be conducted for such Lead Compounds, then on the date of such determination (the "***Candidate Failure Date***"):

(a) None of such Lead Compounds (and all other Compounds included in the applicable Collaboration Program) (each, a "***Failed Candidate***") will be designated a Development Candidate and the applicable Collaboration Target will no longer be a Collaboration Target under this Agreement;

(b) AstraZeneca will not have the right to obtain an exclusive license from Isis to any Failed Candidate in accordance with Section 1.16 below;

(c) If the Failed Candidates are [***] Compounds, the license granted to AstraZeneca under Section 4.1.1 with respect to [***] will automatically terminate;

(d) if and when AstraZeneca timely delivers a Release Notice to Isis, AstraZeneca will be free to Exploit ASOs designed to bind to such former Collaboration Target. If AstraZeneca does not timely deliver a Release Notice to Isis, then for a period of [***] (in the case of [***]) and [***] (in the case of any other Failed Candidate), in each case after the Candidate Failure Date (in each case, the "***Carryover Period***"), AstraZeneca and its Affiliates will not Exploit ASOs designed to bind to such former Collaboration Target other than as research tools in connection with its internal programs;

(e) Isis will be free to Exploit ASOs designed to bind to such former Collaboration Target; *provided however*, that if AstraZeneca does not timely deliver a Release Notice to Isis then:

(i) during the Carryover Period (1) any work Isis conducts on a Failed Candidate (or any other ASO designed to bind to the former Collaboration Target) will be undertaken by Isis for itself and not in collaboration with any Third Party (other than Isis' subcontractors acting for or on behalf of Isis or Isis' academic collaborators) and, (2) except as permitted by this Section 1.14.3(e), Isis will not offer a Failed Candidate to a Third Party; and

(ii) if, within the Carryover Period, Isis intends to commence [***] on a Failed Candidate (or a different ASO designed to bind to the applicable former Collaboration Target), Isis shall notify AstraZeneca and will provide AstraZeneca with the Lead Candidate Data Package for such ASO and AstraZeneca will have an exclusive option (the "***Carryover Option***") to obtain from Isis the license under Section 4.1.1 with respect to such former Collaboration Target. If, within [***] following receipt of such data package, AstraZeneca delivers written notice to Isis that AstraZeneca desires such Target to be restored to this Agreement, such ASO will be deemed to have been designated a Development Candidate by the JSC and AstraZeneca may exercise its rights under Section 1.16 and if the Development Candidate is a [***] Compound the license granted to AstraZeneca for [***] Products under Section 4.1.1 will be automatically restored and effective. If AstraZeneca elects to make such designation and exercises the applicable Collaboration Program License Right, without limiting AstraZeneca's obligation to pay Isis the license fee under Section 6.2 or AstraZeneca's obligation to pay the [***] CD Milestone (as applicable), AstraZeneca will reimburse Isis within [***] of such exercise for [***] ([***]) incurred by Isis with respect to such Development Candidate from the Candidate Failure Date to the date Isis delivered to AstraZeneca the applicable Lead Candidate Data Package under this Section 1.14.3(e)(ii).

(f) Subject to any restoration pursuant to Section 1.14.3(e)(ii) and without limiting Section 4.4.2, Isis will have exclusive rights (and AstraZeneca will, and hereby does grant Isis an exclusive license) to use and practice under the AstraZeneca Collaboration Technology (if any) with respect to such Collaboration Target to Exploit ASOs designed to bind to such former Collaboration Target. For clarity, such grant shall not affect AstraZeneca's right to use and practice under the AstraZeneca Collaboration Technology to Exploit compounds and products in the AstraZeneca Field targeting such former Collaboration Target or to Exploit Compounds that are designed to bind to any remaining Exclusive Target.

(g) With regard to the Jointly-Owned Collaboration Technology for such Collaboration Program, AstraZeneca will assign to Isis all of AstraZeneca's right, title and interest in any Jointly-Owned Product-Specific Patents that do not claim any Compound designed to bind to a remaining Exclusive Target and such other Jointly-Owned Product-Specific Patents as may be agreed by the Parties; and any such transferred Jointly-Owned Product-Specific Patents will be included in the licenses granted by Isis to AstraZeneca under (x) Section 4.4.2 and (y) in so far as they are relevant to a remaining Exclusive Target, Section 4.1.1. On a restoration pursuant to Section 1.14.3(e)(ii), any interest assigned to Isis pursuant to this Section 1.14.3(g), will on AstraZeneca's request be assigned back to AstraZeneca.

(h) Each Party will promptly transfer to the other (to the extent not previously provided) copies of all data, results and information relating to such former Collaboration Targets that it has generated under the Drug Discovery Plan and the other Party shall be entitled to non-exclusively use and disclose such data, results and information in accordance with Section 4.4.

1.14.4. **JSC Process**. The process set forth in this Section 1.14 for the JSC to determine whether a Lead Compound has met the Development Candidate Success Criteria, whether any Lead Compound will be designated a Development Candidate, whether the applicable success criteria will be revised, and/or whether additional work will be conducted for a Lead Compound to be designated as a Development Candidate, will in no event exceed [***] after the date the JSC first convenes the meeting to discuss the Lead Candidate Data Package (or if applicable, the revised Lead Candidate Data Package).

1.15. Expiration of Collaboration Program Term.

1.15.1. **Failure to Designate a Development Candidate**. On a Collaboration Program-by-Collaboration Program basis, if, despite the Parties' Commercially Reasonable Efforts, by the expiration of the Collaboration Program Term, Isis has not delivered a Lead Candidate Data Package for a particular Collaboration Target or the JSC or AstraZeneca has not designated a Development Candidate for a particular Collaboration Target, then:

(a) the Parties will no longer have an obligation to perform any activities under this ARTICLE 1 with respect to such Collaboration Program;

(b) Isis will deliver a Lead Candidate Data Package (completed to the extent possible with the data, results and information generated prior to expiration of the Collaboration Program Term) and the JSC will consider whether any Lead Compound from such Collaboration Program has met the applicable Development Candidate Success Criteria, and whether or not such criteria are met AstraZeneca may designate such a Compound a Development Candidate by delivering a written notice to Isis of such designation within [***] after AstraZeneca's receipt of such Lead Candidate Data Package;

(c) unless AstraZeneca designates a Development Candidate for a particular Collaboration Program pursuant to Section 1.15.1(b), all Compounds from such Collaboration Program will be deemed to be Failed Candidates and Section 1.14.3 will apply.

1.15.2. **Status of other Collaboration Programs**. For clarity, the expiration of the Collaboration Program Term will not affect the Parties' respective rights and obligations with respect to any Collaboration Program that, at the end of the Collaboration Program Term (a) is a Licensed Program; or (b) is being evaluated by AstraZeneca pursuant to Section 1.16 until the expiry of the applicable Collaboration Program License Right Deadline.

1.16. Exclusive Right to Obtain or Maintain Exclusive Licenses to Development Candidates.

1.16.1. **Collaboration Program License Rights**. On a Collaboration Target-by-Collaboration Target basis, AstraZeneca has the exclusive right which it may exercise at any time on or before 5:00 p.m. (Pacific time) on the [***] (each, a "***Collaboration Program License Right Deadline***" and such period the "***Evaluation Period***") following the date [***] (each, a "***Collaboration Program License Right***") to (i) with respect to a Collaboration Target that is not [***], obtain from Isis the license set forth in Section 4.1.1 below, or (ii) with respect to [***], maintain the exclusive license set forth in Section 4.1.1.

1.16.2. **AstraZeneca Evaluation**. During and prior to the Evaluation Period, AstraZeneca may conduct other activities at its expense to supplement the information it uses to determine if it wishes to designate the Development Candidate as a Candidate Drug (in accordance with AstraZeneca's internal procedures) and exercise its Collaboration Program License Right. After designation of a Development Candidate, Isis will provide AstraZeneca as promptly as practicable with [***] of non-GMP research grade API of such Development Candidate (or applicable rodent ASO Isis designed under the applicable Drug Discovery Plan), [***]; *provided, that*, if Isis cannot provide such research grade API to AstraZeneca within [***] after designation of such Development Candidate, the applicable Collaboration Program License Right Deadline and Evaluation Period will be extended for an amount of time equal to the number of days thereafter that it takes Isis to deliver such research grade API to AstraZeneca. If requested by AstraZeneca during the Evaluation Period, and in Isis' possession, Isis will supply further quantities of non-GMP research grade API at [***]. AstraZeneca will notify Isis whether AstraZeneca is exercising its Collaboration Program License Right to license the applicable Collaboration Target or maintain its license to [***] (and in each case all Products included in the applicable Collaboration Program) by notifying Isis in writing on or before the applicable Collaboration Program License Right Deadline. During such Evaluation Period, AstraZeneca will keep Isis apprised of AstraZeneca's progress in making a decision regarding such exercise to enable Isis to plan as early as possible for manufacturing of API under Section 5.5 for the relevant Development Candidate for [***]. For each Collaboration Program being evaluated, during such Evaluation Period Isis will provide such information as AstraZeneca may reasonably request in connection with such evaluation [***].

1.16.3. **Exercise**. If AstraZeneca notifies Isis in writing by the Collaboration Program License Right Deadline that AstraZeneca is exercising the Collaboration Program License Right (on a Collaboration Program-by-Collaboration Program basis, the date of such notice, the "***Collaboration Program Exercise Date***"), AstraZeneca will pay Isis the license fee set forth in Section 6.2 or the [***] CD Milestone set forth in Section 6.3 (as applicable) within [***] after AstraZeneca's receipt of an invoice from Isis for such payment, and, (a) if the Collaboration Program is [***], the license in Section 4.1.1 shall continue and (b) in the case of a Collaboration Program that is not the [***] Program, Isis will, and hereby does, grant to AstraZeneca the license set forth in Section 4.1.1 below with respect to such Collaboration Program.

1.16.4. **No Exercise**. On a Collaboration Program-by-Collaboration Program basis, if AstraZeneca does not provide timely written notice to Isis under Section 1.16.3, then:

(a) AstraZeneca's Collaboration Program License Right will expire and no license fee is payable under Section 6.2, and AstraZeneca will have no further rights to (and Isis will have no further obligations with respect to) such Collaboration Target (including the Development Candidate and all other Compounds included in the applicable Collaboration Program);

(b) the Target to which such Compounds are directed will cease to be a Collaboration Target;

(c) if the Collaboration Target is [***], no [***] CD Milestone is payable, and the license granted to AstraZeneca under Section 4.1.1 for [***] Products will automatically terminate;

(d) Isis will have exclusive rights (and AstraZeneca will, and hereby does grant Isis an exclusive license) to the AstraZeneca Collaboration Intellectual Property (if any) generated by AstraZeneca under this Agreement for such Collaboration Target to Exploit ASOs designed to bind to such Collaboration Target. For clarity, such grant will not affect AstraZeneca's right to use and practice under the AstraZeneca Collaboration Technology to Exploit compounds and products in the AstraZeneca Field targeting such former Collaboration Target or to Exploit Compounds that are designed to bind to any remaining Exclusive Target.

(e) With regard to the Jointly-Owned Collaboration Technology for such Collaboration Program, AstraZeneca will assign to Isis all of AstraZeneca's right, title and interest in any Jointly-Owned Product-Specific Patents that do not claim any Compound designed to bind to a remaining Exclusive Target and such other Jointly-Owned Product-Specific Patents as may be agreed by the Parties; and any such transferred Jointly-Owned Product-Specific Patents will be included in the licenses granted by Isis to AstraZeneca under (x) Section 4.4.2 and (y) in so far as they are relevant to a remaining Exclusive Target, Section 4.1.1.

(f) Each Party will promptly transfer to the other (to the extent not previously provided) copies of all data, results and information relating to such former Collaboration Targets that it has generated under the Drug Discovery Plan and the other Party shall be entitled to non-exclusively use and disclose such data, results and information in accordance with Section 4.4;

(g) for a period of [***] thereafter, AstraZeneca and its Affiliates will not develop or commercialize an ASO designed to bind to the applicable former Collaboration Target other than as research tools in connection with its internal programs; and

(h) to the extent not previously provided, AstraZeneca will promptly transfer to Isis copies of all data, results and information generated by AstraZeneca related to the testing and studies with respect to the applicable Collaboration Target undertaken by AstraZeneca during, and prior to, the Evaluation Period.

ARTICLE 2.
COLLABORATION MANAGEMENT; ADMINISTRATION; COSTS AND EXPENSES AND MANUFACTURING

2.1. Collaboration Management.

2.1.1. **JSC**. The Parties will establish a joint steering committee ("***JSC***") for the Collaboration Programs within [***] of the Effective Date, to finalize and update the Collaboration Plans and oversee the conduct of activities under the respective Collaboration Plans. The JSC will consist of four representatives appointed by Isis and four representatives appointed by AstraZeneca. Each JSC member will be a senior research or development leader or have similar experience and expertise as a senior research or development leader. Each Party will designate one of its four representatives who are 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 each JSC. The co-chairs will be responsible for overseeing the activities of its JSC consistent with the responsibilities set forth in Section 2.1.2. SCHEDULE 2.1.1 sets forth certain JSC governance matters agreed to as of the Execution Date. The JSC will determine the JSC operating procedures at its first meeting, including the JSC's policies for replacement of JSC members, policies for participation by additional representatives or consultants invited to attend JSC meetings, and the location of meetings, which will be codified in the written minutes of the first JSC meeting. Each Party will be responsible for the costs of its own employees or consultants attending JSC meetings.

2.1.2. **Role of the JSC**. Without limiting any of the foregoing, the JSC will perform the following functions in accordance with this Agreement, some or all of which may be addressed directly at any given JSC meeting:

(a) review and agree on the Core Research Plan and any amendments thereto;

(b) review and agree on the Disease Research Plan and any amendments thereto taking into account the outline in SCHEDULE 1.2.2 and the requirement to achieve the criteria and perform the activities listed in SCHEDULE 1.8;

(c) [***];

(d) regularly discuss potential Eligible Targets and the application of the Exclusion Criteria to such Targets and maintain the Reserved Target List in the minutes of the JSC;

(e) establish criteria and a process for selecting and prioritizing High Interest Targets;

(f) maintain the list of High Interest Targets in the minutes of the JSC;

(g) determine the High Interest Targets to be worked on in the Disease Research Plan and when work on a High Interest Target is to commence;

(h) set the Target Sanction criteria for each High Interest Target under the Disease Research Plan; *provided that* unless otherwise agreed by the JSC, such criteria shall include the criteria listed in SCHEDULE 1.8;

(i) evaluate each Target Sanction Data Package and make a determination regarding whether a High Interest Target has achieved Target Sanction status, whether a High Interest Target will be designated a Collaboration Target, whether the Target Sanction criteria will be revised, and/or whether additional work will be conducted for such High Interest Target to achieve Target Sanction as further provided in Section 1.10;

(j) maintain the list of Collaboration Targets that are the subject of the Collaboration Programs;

(k) agree on the Drug Discovery Plan for each Collaboration Program;

(l) prepare Work Plan Reports in accordance with Section 2.7;

(m) evaluate each Lead Candidate Data Package and make a determination regarding whether any Lead Compound has met the Development Candidate Success Criteria, whether a Lead Compound will be designated a Development Candidate, whether such success criteria will be revised, and/or whether additional work will be conducted for such Lead Compound to be designated as a Development Candidate as further provided in Section 1.14;

(n) review the overall progress of the activities under the applicable Collaboration Plan;

(o) review, provide advice on, and amend the applicable Collaboration Plan; and

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

2.1.3. Collaboration Program Decision Making.

(a) If the JSC cannot unanimously agree on a matter to be decided by the JSC, then either Party shall have the right to refer such dispute to the Senior Representatives for resolution by good faith negotiations in accordance with Section 12.1.1. The Parties shall not implement the proposed activity or change pending such decision of the Senior Representatives; *provided that* if the dispute relates to a proposed change to a Collaboration Plan previously agreed by the JSC, Isis may continue the Isis Conducted Activities in accordance with such plan pending resolution of the dispute by the Senior Representatives.

(b) Notwithstanding any provision to the contrary herein, Isis will have no obligation to perform any activity that, after having consulted the JSC, Isis in good faith believes that continuing such activity would (y) [***] or (z) [***].

2.1.4. **Term of the JSC**. Isis' obligation to participate in relation to a Collaboration Plan in the JSC will terminate on the date Isis completes all the Isis Conducted Activities under such Collaboration Plan. Thereafter, Isis will have the right, but not the obligation, to participate in the JSC meetings in relation to such Collaboration Plan upon Isis' request. After [***], the JSC will cease to be responsible for making decisions with respect to such [***] (and for the avoidance of doubt, without limiting the foregoing, the provisions of Section 2.1.3(a) will cease to apply) and AstraZeneca will have full decision making authority with respect to such [***] subject to AstraZeneca's continuing obligation to use Commercially Reasonable Efforts under this Agreement. The JSC will become a forum for the Parties to share information regarding the Licensed Program, and the Parties will decide on the number and frequency of meetings required of the JSC in respect of such Licensed Program in its new role.

2.2. **Alliance Managers**. Promptly after the Effective Date each Party will appoint a representative to act as its alliance manager (each, an "***Alliance Manager***"). Each Alliance Manager will be permitted to attend any meetings of the JSC, and to participate in such meetings as a non-voting observer (unless the Party appointing the Alliance Manager also appoints such person to be a member of the JSC). The Alliance Managers will be responsible for supporting the JSC and performing the activities listed in SCHEDULE 2.2. Each Party may replace its Alliance Manager at any time upon written notice to the other Party in accordance with Section 12.7. During the Collaboration Program Term, the Alliance Managers will meet on a monthly basis (or more frequently as they may determine), in person or telephonically, to discuss the progress of the various activities under the Collaboration Plans.

2.3. **Disclosure of Results**.

2.3.1. **Results under the Collaboration Plans**. Each Party will promptly disclose to the other Party the results of all work performed by the Parties under the Collaboration Plans in a reasonable manner as such results are obtained. Isis and AstraZeneca will provide reports and analyses at each JSC meeting, and more frequently on reasonable request by any member of the JSC, detailing the current status of each Collaboration Plan.

2.3.2. **Reporting by AstraZeneca for Licensed Programs**. For each Licensed Program, AstraZeneca will prepare and maintain reasonably complete and accurate records regarding the Development of each Product and will provide to Isis a reasonably detailed summary report of such activities at least [***], or sooner if [***] (i.e., [***]), a material interaction with a Regulatory Authority occurs with respect to a Product, or [***]. AstraZeneca shall prepare such report in accordance with its internal procedures. AstraZeneca's obligation to provide such information shall cease in accordance with Section 5.2.

2.3.3. **Use of Information**. The results, reports, analyses and other information regarding the Collaboration Plans disclosed by one Party to the other Party pursuant hereto may be used only in accordance with the rights granted and other terms and conditions under this Agreement.

2.3.4. **Format of Reporting**. Any reports required under this Section 2.3 may take the form of and be recorded in minutes of the JSC, which will contain copies of any slides relating to the results as presented to the JSC.

2.4. **Materials Transfer**.

2.4.1. In order to facilitate the activities under the Collaboration Plans, either Party may provide to the other Party certain materials for use by the other Party in furtherance of the Collaboration Plans. All such materials will be used by the receiving Party in accordance with the terms and conditions of this Agreement solely for purposes of exercising its rights and performing its obligations under this Agreement, and the receiving Party will not transfer such materials to any Third Party unless expressly contemplated by this Agreement or upon the written consent of the supplying Party.

2.4.2. The Parties acknowledge and agree that they will exchange information regarding the materials used or generated in connection with the Research Collaboration and if requested by the other Party, each will use reasonable endeavors (subject to its own requirements and any obligations owed to Third Parties) to provide or assist the other to obtain, in the case of AstraZeneca, materials that are Isis Collaboration Intellectual Property, and in the case of Isis, materials that are AstraZeneca Collaboration Intellectual Property, in each case for use in accordance with Section 4.4.

2.4.3. Except as expressly set forth herein, THE MATERIALS ARE PROVIDED "AS IS" AND WITHOUT ANY REPRESENTATION OR WARRANTY, EXPRESS OR IMPLIED, INCLUDING ANY IMPLIED WARRANTY OF MERCHANTABILITY OR OF FITNESS FOR ANY PARTICULAR PURPOSE OR ANY WARRANTY THAT THE USE OF THE MATERIALS WILL NOT INFRINGE OR VIOLATE ANY PATENT OR OTHER PROPRIETARY RIGHTS OF ANY THIRD PARTY. [***]

2.5. **Collaboration Costs**.

2.5.1. **Core Research Program Costs and Disease Research Program Costs**. During the Core Research Term and the Disease Research Term, subject to Section 1.10, Isis will be responsible for all costs associated with the Isis Conducted Activities designated under the Core Research Plan and the Disease Research Plan, and AstraZeneca will be responsible for all costs associated with any AstraZeneca Conducted Activities designated under the Core Research Plan and the Disease Research Plan.

2.5.2. Collaboration Program Costs.

(a) **Drug Discovery Plan Costs Paid by Isis**. Until AstraZeneca exercises the Collaboration Program License Right for a particular Collaboration Program, unless otherwise specified in Section 1.14 and except as otherwise provided under Section 2.5.2(b), Isis will be responsible for all costs associated with the Isis Conducted Activities designated under each Drug Discovery Plan.

(b) **Drug Discovery Plan and Other Costs Paid by AstraZeneca**.

(i) **Before Exercising a Collaboration Program License Right**. Until AstraZeneca exercises the Collaboration Program License Right for a particular Collaboration Program, unless otherwise specified in Section 1.14, AstraZeneca will be responsible for all costs associated with the AstraZeneca Conducted Activities designated under each Drug Discovery Plan.

(ii) **After Exercising a Collaboration Program License Right**. After AstraZeneca exercises the Collaboration Program License Right for a particular Collaboration Program, AstraZeneca will be solely responsible for the costs related to the Research, Development, Manufacture and Commercialization of Products, including all AstraZeneca Conducted Activities.

2.6. **Collaboration Manufacturing and Supply**. [***], Isis will supply API sufficient to support the Isis Conducted Activities and the AstraZeneca Conducted Activities designated under a given Collaboration Plan. [***]

2.7. **JSC Collaboration Summary Work Plan Reports**. On a Calendar Quarter-by-Calendar Quarter basis, beginning with the [***], within [***] after the end of the most recent Calendar Quarter, the JSC (with the assistance of the Alliance Managers) will deliver a written report to AstraZeneca which identifies, for each Collaboration Target, the [***] (each a "***Work Plan Report***") as agreed by the JSC. Where planned activities under the Collaboration Plans for a Collaboration Target have not yet been agreed by the JSC, no data will be provided. The report template is included in SCHEDULE 2.7. The information in the report on [***] will provide the basis for [***]. Such reports will be prepared throughout the Collaboration Program Term until [***]. AstraZeneca will notify the JSC if Work Plan Reports are no longer required during the Collaboration Program Term.

2.8. **Applicable Laws and Bioethics**. The Research to be conducted by each Party (including by its subcontractors) pursuant to this Agreement will be carried out in good scientific manner, and in compliance with all Applicable Laws. In addition, each Collaboration Program will be carried out in compliance with the AstraZeneca bioethics policy attached at SCHEDULE 2.8, to attempt to achieve efficiently and expeditiously the objectives of the applicable Collaboration Plan. In respect of any Isis Conducted Activities to be initiated under a Collaboration Program after the Effective Date, Isis and AstraZeneca will mutually agree on [***] and, prior to award of the work, will work together to secure compliance with AstraZeneca's bioethics policy. Where a [***], the Parties will discuss and agree whether such [***]. Insofar as the requirements of complying with such policy will result in additional [***] costs being charged to Isis for work [***] for Isis Conducted Activities, compared to [***], AstraZeneca agrees to be responsible for such additional costs [***]. The Parties will agree when such costs will be invoiced by Isis and AstraZeneca will pay such costs to Isis within 60 days after AstraZeneca's receipt of an invoice from Isis. The Parties' discussion and agreement under this Section 2.8 can be through the JSC.

ARTICLE 3.
EXCLUSIVITY COVENANTS

3.1. **Exclusivity Covenants**.

3.1.1. **Isis' and AstraZeneca's Exclusivity Covenants**. On an Exclusive Target-by-Exclusive Target basis, except in the performance of its obligations or exercise of its rights under, in the case of AstraZeneca, Section 4.1, and in the case of Isis, Section 10.3.2(a), or as set forth in Section 3.1.2 or Section 3.1.3, Isis and AstraZeneca will not work independently or for or with any of its Affiliates or any Third Party (including the grant of any license to any Third Party) with respect to:

(a) ***High Interest Targets***. The discovery, research or development of an ASO that is designed to bind to any of the High Interest Targets, from the date each such Target becomes a High Interest Target under Section 1.7.1 until [***];

(b) ***Collaboration Targets During the Collaboration Program License Right Period***. The discovery, research or development of an ASO that is designed to bind to any Collaboration Target, from the date each Collaboration Target is or deemed to have been designated by the JSC until [***] (x) [***], (y) [***], or (z) [***]; and

(c) ***Collaboration Targets After Exercising the Collaboration Program License Right***. The development or commercialization, in the Field, of an ASO that is designed to bind to a Collaboration Target for which AstraZeneca has exercised its Collaboration Program License Right in accordance with this Agreement, (A) with respect to development of an ASO that is designed to bind to such Collaboration Target, until [***] or [***], and (B) on a country–by-country basis with respect to commercialization of an ASO that is designed to bind to such Collaboration Target in the Field, until [***].

3.1.2. **Isis Follow-On Products**. Notwithstanding the provisions of Section 3.1.1, on an Exclusive Target-by-Exclusive Target basis, if (A) AstraZeneca does not ask Isis to identify a follow-on product for an Exclusive Target [***] for a Product, or (B) Isis identifies a follow-on product for an Exclusive Target at AstraZeneca's request, but thereafter AstraZeneca does not use Commercially Reasonable Efforts to continue to develop and commercialize such follow-on compound, then Isis (for itself or with or for a Third Party) will be permitted to (i) discover, research and develop an ASO designed to bind to such Exclusive Target that is not the Product being developed by AstraZeneca (an "***Isis Follow-On Product***"), and (ii) after [***] for a Product, commercialize such Isis Follow-On Product.

3.1.3. **Limitations and Exceptions to Each Party's Exclusivity Covenants**.

(a) **Limitations and Exceptions to Isis' Exclusivity Covenants**. Notwithstanding anything to the contrary in this Agreement, Isis' practice of the following will not violate Section 3.1.1 or Section 3.1.2:

(i) Performance of the Isis Conducted Activities;

(ii) With respect to any Collaboration Target, any activities permitted under the Prior Agreements as such agreements are in effect on the date the Target is put on the High Interest Target List and have been disclosed to AstraZeneca (and not as such Prior Agreements may be amended thereafter); and

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

(b) **Other Limitations and Exceptions to AstraZeneca's Exclusivity Covenants**. Notwithstanding anything to the contrary in this Agreement, AstraZeneca's performance of the AstraZeneca Conducted Activities will not violate Section 3.1.1 or Section 3.1.2.

3.2. **Additional Exclusivity Covenants**. The Parties acknowledge and agree that the exclusivity covenants set forth in Section 3.1 above are in addition to and do not limit AstraZeneca's covenants set forth in Section 1.10.3, Section 1.14.3 and Section 1.16.4.

3.3. **Corporate Transactions**. Notwithstanding anything to the contrary in this Agreement, Isis will not be in breach of Section 3.1.1 or Section 3.1.2 and AstraZeneca will not be in breach of Section 3.1.1 or the covenants set forth in Section 1.10.3, Section 1.14.3 or Section 1.16.4 as a result of activities relating to an ASO designed to bind to an Exclusive Target (each a "***Competitive ASO***") or a program relating to Competitive ASOs, in each case resulting from the direct or indirect acquisition by a Third Party of a Party or the direct or indirect acquisition by a Party or one of its Affiliates of a Third Party (including through an acquisition of substantially all of its business), in each case after the Execution Date; *so long as:*

3.3.1. in the case where a Party is acquired by a Third Party (the "***Acquiring Party***") with a Competitive ASO, the activities relating to the discovery, research, development or commercialization of the Competitive ASO by the Acquiring Party [***]; or

3.3.2. in the case where a Party or its Affiliate acquires a Third Party (the "***Acquisition Target***") with a Competitive ASO, [***] the acquiring Party or its Affiliate and the Acquisition Target either (i) [***], (ii) [***], (iii) in the case of AstraZeneca, [***], or (iv) [***].

If the Party so acquired or involved in the acquisition of a Competitive ASO is Isis, Section 5.2 will apply (pending, in the case of Section 3.3.2, such [***].

3.4. **Effect of Exclusivity on Indications**. The Compounds are designed to bind to the Exclusive Targets in the Field, which are known to play a role in one or more Primary Diseases. Isis and AstraZeneca are subject to exclusivity obligations under Section 3.1.1 and Section 3.1.2; *however*, the Parties acknowledge and agree that each Party (on its own or with a Third Party) may continue to discover, research, develop, manufacture and commercialize products that are designed to bind to a Target that is *not* an Exclusive Target, for any indication, even if such products are designed to treat a Primary Disease.

ARTICLE 4.
LICENSE GRANTS; TECHNOLOGY TRANSFER AND SUPPORT

4.1. **Product License Grants to AstraZeneca**.

4.1.1. **Collaboration Target Development and Commercialization Licenses**. On a Collaboration Target-by-Collaboration Target basis, subject to the terms and conditions of this Agreement:

(a) Isis hereby grants AstraZeneca a worldwide, exclusive (including with regard to Isis and its Affiliates), perpetual and irrevocable (except as otherwise expressly provided in this Agreement), 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) and Commercialize [***] Products in the Field; and

(b) in the case of a Collaboration Target that is not [***], grants to AstraZeneca effective upon AstraZeneca's exercise of the Collaboration Program License Right for such Collaboration Target in accordance with Section 1.16, a worldwide, exclusive (including with regard to Isis and its Affiliates), perpetual and irrevocable (except as otherwise expressly provided in this Agreement), 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) and Commercialize Products with respect to such Collaboration Target in the Field.

4.1.2. Sublicense Rights.

(a) **Right to Grant Sublicenses**. Subject to the terms and conditions of this Agreement, AstraZeneca will have the right to grant sublicenses through multiple tiers of sublicenses under the licenses granted under Section 4.1.1 above:

(i) under the Licensed Technology (other than Isis Manufacturing and Analytical Patents and Isis Manufacturing and Analytical Know-How), to an Affiliate of AstraZeneca or a Third Party; and

(ii) under the Isis Manufacturing and Analytical Patents and Isis Manufacturing and Analytical Know-How solely to (y) an Affiliate of AstraZeneca or (z) a Third Party with a valid license granted by Isis under the Isis Manufacturing and Analytical Patents and Isis Manufacturing and Analytical Know-How to manufacture Products in a manufacturing facility owned or operated by such Third Party (each, a "***Licensed CMO***");

provided that each such sublicense is for the continued Development, Manufacture and/or Commercialization of a Product, and is subject to, and consistent with, the terms and conditions of this Agreement. AstraZeneca will use reasonable efforts to ensure that all Persons to which it grants sublicenses comply with such terms and conditions to the extent applicable to such sublicense. For clarity, the restrictions in this Section 4.1.2 shall not apply to the appointment of Third Parties who undertake additional manufacturing activities, including testing, and fill/finish using API supplied by or on behalf of AstraZeneca; *provided that* such Third Party is undertaking such activities for AstraZeneca, its Affiliates or Sublicensees and no Licensed Know-How is transferred to such Third Party.

(b) **Enforcing Sublicense Agreements**. If either Party learns of a Sublicensee's breach of the terms of a sublicense granted by AstraZeneca, such Party will promptly notify the other Party in writing and will provide such other Party with any available evidence of such breach, and the Parties will discuss in good faith any applicable cure. AstraZeneca will have the first right to enforce the terms of the sublicense against such Sublicensee and demand the Sublicensee cure such breach. If, within [***] after the discussion with Isis regarding an applicable cure, AstraZeneca fails to take action as discussed by Isis and AstraZeneca to enforce the sublicense terms of a sublicense granted pursuant to this Section 4.1.2 and effect the applicable cure, which failure, in Isis' good faith determination as notified to AstraZeneca in writing, might reasonably be expected to cause a [***], AstraZeneca hereby grants Isis the right to enforce such sublicense terms on AstraZeneca's behalf and will cooperate with Isis (which cooperation will be at AstraZeneca's sole expense and will include, AstraZeneca 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. AstraZeneca will provide Isis with written notice of any sublicense granted pursuant to this Section 4.1.2 that grants a Third Party rights to Commercialize or manufacture a Product, within [***] after the execution thereof, and if requested by Isis, a true and complete copy of any such sublicense or any sublicense that is the subject of a breach of terms sublicensed under this Agreement within 10 days of Isis' request, subject to AstraZeneca being entitled to make appropriate redaction for commercially sensitive information provided it is not relevant to enforcement or is not reasonably necessary for Isis to determine AstraZeneca's compliance with the terms of this Agreement.

(c) **Requests to Grant Sublicenses to CMOs**. In addition, if AstraZeneca provides Isis with a written request that Isis grant a license under the Isis Manufacturing and Analytical Patents and Isis Manufacturing and Analytical Know-How to a CMO designated by AstraZeneca that is not a Licensed CMO, solely for such CMO to manufacture Products for AstraZeneca, its Affiliate or Sublicensee in a manufacturing facility owned or operated by such CMO, Isis will offer to grant such a license to such CMO on terms that are substantially similar to the terms Isis has previously agreed to with its Licensed CMOs. On entering into such an agreement with Isis, such CMO shall become a Licensed CMO for the purpose of Section 4.1.2(a)(ii).

(d) **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 AstraZeneca; *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 AstraZeneca, 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 AstraZeneca. AstraZeneca agrees that it will confirm to its knowledge clause (i) of the foregoing in writing at the request and for the benefit of Isis and if requested, the Sublicensee.

(e) **Master Services Agreements and Material Transfer Agreements**. This Section 4.1.2 is not intended to require AstraZeneca to amend the standard terms and conditions of a master services agreement with a Third Party in place as of the Execution Date to conduct preclinical and/or clinical Research and Development on AstraZeneca's behalf, or material transfer agreements with academic collaborators or non-profit institutions, entered into after the Execution Date by AstraZeneca in connection with the Licensed Technology. However, new agreements entered into after the Execution Date will be subject to the approval of the JSC for so long as the JSC has decision making authority, such approval not to be unreasonably withheld or delayed; *provided that* no such approval will be required or given until after the Effective Date.

(f) **Fees Payable by CMOs**. Isis hereby agrees that Licensed CMOs or a CMO licensed pursuant to a request by AstraZeneca pursuant to Section 4.1.2(c) shall not be required to pay any license fees or royalties to Isis in connection with the manufacture of Products for AstraZeneca that are licensed to AstraZeneca under Section 4.1.1.

4.1.3. **Consequence of Natural Expiration of this Agreement**. On a Product-by-Product basis, if with respect to a particular Product for which AstraZeneca has exercised the applicable Collaboration Program License Right, this Agreement expires (i.e., is not terminated early) in a particular country in accordance with Section 10.1 then, in addition to the terms set forth in Section 10.3.1(c), Section 10.3.1(f), Section 10.3.1(g) and Section 10.3.1(h), the applicable license under Section 4.1.1 to the Licensed Know-How for such Product will automatically convert into a perpetual, non-exclusive, worldwide, royalty-free, fully paid-up, sublicensable license under the Licensed Know-How to Manufacture, Research, Develop and Commercialize the Product that is the subject of such expiration in such country.

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

4.1.5. **License Conditions; Limitations**. Subject to Section 6.8 and Section 6.9, on a Collaboration Target-by-Collaboration Target basis, the licenses granted under Section 4.1.1 and the sublicense rights under Section 4.1.2 are subject to and limited by (i) the Prior Agreements as such agreements are in effect on the date such Collaboration Target was designated as a High Interest Target and placed on the High Interest Target List (or, with respect to [***], the Execution Date) and have been disclosed to AstraZeneca prior to such date (and not as such Prior Agreement may be amended thereafter), (ii) the Isis In-License Agreements as such agreements are in effect on the date identified as Isis In-License Agreements and added to APPENDIX 3 as provided in Section 6.8.5 (and in the form disclosed to AstraZeneca prior to such date and not as such Isis In-License Agreements may be amended thereafter unless such amendment is made with AstraZeneca's prior written consent); and (iii) the granting of, or performance of obligations under, Permitted Licenses.

4.1.6. **Trademarks for Products**. To the extent that (i) Isis owns any trademark(s) specific to a Product licensed under Section 4.1.1, and (ii) AstraZeneca reasonably believes such trademark(s) are necessary or useful for such Product, then upon AstraZeneca's request and at AstraZeneca's sole cost and expense, Isis will assign its rights and title to such trademark(s) to AstraZeneca sufficiently in advance of the First Commercial Sale of a Product. Other than any such trademarks, AstraZeneca is solely responsible for all trademarks, trade dress, logos, slogans, designs, copyrights and domain names used on or in connection with Products licensed under Section 4.1.1.

4.1.7. [***]

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

4.2.1. On a Collaboration Target-by-Collaboration Target basis, with respect to any Collaboration Target for which AstraZeneca has an exclusive license under Section 4.1.1, at any time after completion of the first Phase 2 Study for the applicable Product, after discussion by the IP Managers, Isis will assign to AstraZeneca (and AstraZeneca will accept from Isis), Isis' ownership interest in all Isis Product-Specific Patents within the Licensed Patents that are owned by Isis (whether solely owned or jointly owned with one or more Third Parties); *provided that*, if either Party reasonably determines that such assignment would be likely to adversely affect the applicable Licensed Patent (including diminishing the scope, term, validity or enforceability of such Licensed Patent), then, [***].

4.2.2. AstraZeneca grants to Isis a worldwide, exclusive, sublicensable license under any Patent Rights assigned to AstraZeneca under Section 4.2.1 (i) for all purposes outside of the Field (except to license or Commercialize a compound claimed by the Product-Specific Patents that specifically claim the Product being Developed and Commercialized by AstraZeneca), and (ii) to research, develop, manufacture, have manufactured, register, market and commercialize Isis Follow-On Products in accordance with Section 3.1.2, in each case to the extent permitted by this Agreement.

4.3. **Non-Exclusive Technology License Grant to AstraZeneca**. As of the Effective Date, subject to the terms and conditions of this Agreement, Isis hereby grants to AstraZeneca a worldwide, non-exclusive, non-sublicenseable, non-transferrable, royalty-free, fully-paid up, license under the Isis Collaboration Intellectual Property and Isis Background Intellectual Property, for the sole purpose of AstraZeneca (i) performing the AstraZeneca Conducted Activities and effectively participating in the JSC under this Agreement, (ii) to understand and retain some capabilities with regard to Isis' technology in furtherance of AstraZeneca's continuation of the Development of Products under this Agreement after expiration of Isis' input (e.g., post-AstraZeneca exercise of each Collaboration Program License Right) (but expressly excluding the right to Manufacture or Commercialize such Products), (iii) conducting research activities outside the scope of this Agreement that are not human clinical studies or designed to support an IND and do not involve any Compounds being developed or commercialized by Isis, its Affiliates or sublicensees on its or their own behalf, and (iv) solely with respect to Product-Specific Patents within the Isis Technology and Isis Background Technology, conducting research and development activities in the AstraZeneca Field. Except as expressly provided in clauses (i) and (ii) of this Section 4.3, the foregoing license granted to AstraZeneca in this Section 4.3 does not include the right to Develop, Manufacture or Commercialize a Compound.

4.4. **Cross-Licenses Under Collaboration Intellectual Property**.

4.4.1. **Enabling Technology Licenses from AstraZeneca to Isis**. Subject to the terms and conditions of this Agreement (including Isis' exclusivity obligations under Section 3.1), AstraZeneca hereby grants Isis a fully-paid, royalty-free (except as otherwise provided under Section 10.3.2(g) and Section 10.3.2(h)), irrevocable, worldwide, non-exclusive, sublicenseable license under any AstraZeneca Collaboration Intellectual Property (including AstraZeneca's interest in any Jointly-Owned Collaboration Technology) to research, develop, manufacture, have manufactured and commercialize products (other than any ASO designed to bind to an Exclusive Target) in the Isis Field.

4.4.2. **Enabling Technology Licenses from Isis to AstraZeneca**. Subject to the terms and conditions of this Agreement, Isis hereby grants AstraZeneca a fully-paid, royalty-free, irrevocable, worldwide, non-exclusive, sublicenseable license under any Isis Collaboration Intellectual Property (including Isis' interest in any Jointly-Owned Collaboration Technology) to research, develop, manufacture, have manufactured and commercialize products in the AstraZeneca Field.

4.5. **Interaction of Licenses.** For the avoidance of doubt, the licenses granted in Section 4.3 and Section 4.4 are not intended to undermine the exclusivity covenants or the exclusive nature of any exclusive licenses granted to a Party under this Agreement, or any of the royalty-bearing licenses granted by one Party to the other Party under Section 4.1.1 or Section 10.3.2(a). As such, a Party cannot attempt to exercise a right granted under Section 4.3 or Section 4.4 to avoid complying with an applicable exclusivity covenant, or paying a milestone payment, royalty or other payment that would be due under this Agreement as a result of exercising rights under the licenses granted under Section 4.1.1 or Section 10.3.2(a).

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 this Agreement will meet the qualifications typically required by such Party for the performance of work similar in scope and complexity to the subcontracted activity and will enter into such Party's standard nondisclosure agreement consistent with such Party's standard practices. Any Party engaging a subcontractor hereunder will remain responsible and obligated for such activities and will not grant rights to such subcontractor that interfere with the rights of the other Party under this Agreement.

4.7. **[***] Initial Technology Transfer.** To the extent not previously provided, within [***] of the Effective Date, Isis will deliver or otherwise make available (through site visits or access to shared electronic portals) to AstraZeneca the Licensed Know-How relating to the [***] Program as conducted by Isis prior to the Effective Date, for use solely in accordance with the licenses granted under Section 4.1.1(a) and Section 4.3.

4.8. **Technology Transfer**. On a Collaboration Target-by-Collaboration Target basis, after the Collaboration Program Exercise Date, Isis will deliver to AstraZeneca the following Licensed Know-How pursuant to a technology transfer plan to be mutually agreed by Isis and AstraZeneca:

4.8.1. **Licensed Know-How - Generally**. Copies of Licensed Know-How (other than the Isis Manufacturing and Analytical Know-How) in the Field 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 4.3, to AstraZeneca together with all regulatory documentation (including drafts, if any) related to each Product. To assist with the transfer of such Licensed Know-How, Isis will make its personnel reasonably available to AstraZeneca during normal business hours for up to a total (i.e., not on a Collaboration Target-by-Collaboration Target basis) of [***] ([***]) of Isis' time under this Agreement to transfer such Licensed Know-How under this Section 4.8.1. Thereafter, if requested by AstraZeneca, Isis will provide AstraZeneca with a reasonable level of assistance in connection with such transfer, which AstraZeneca will reimburse Isis for its time incurred in providing such assistance at the FTE Rate, and any of Isis' reasonable travel expenses for travel requested by AstraZeneca, and any outside consultants' costs and consultants' reasonable travel expenses incurred by Isis agreed in advance by AstraZeneca.

4.8.2. **Isis Manufacturing and Analytical Know-How**. Solely for use by AstraZeneca, its Affiliates or a Third Party acting on AstraZeneca's behalf to Manufacture API for AstraZeneca, its Affiliates or Sublicensees, in AstraZeneca's own, or an Affiliate's, or up to two mutually agreed Licensed CMO's manufacturing facility, copies of the Isis Manufacturing and Analytical Know-How relating to Products in Isis' possession that has not previously been provided hereunder, which is necessary for the exercise by AstraZeneca, its Affiliates or a Third Party of the Manufacturing rights granted under Section 4.1.1. Isis will make its personnel reasonably available to AstraZeneca during normal business hours and AstraZeneca will reimburse Isis for its time incurred in performing such technology transfer at the FTE Rate, and any of Isis' reasonable travel expenses for travel requested by AstraZeneca, and any of its outside consultants' costs and consultants' reasonable travel expenses incurred by Isis agreed in advance by AstraZeneca.

ARTICLE 5.
DEVELOPMENT, MANUFACTURING AND COMMERCIALIZATION

5.1. **AstraZeneca Diligence**. On a Collaboration Target-by-Collaboration Target basis, commencing on the Collaboration Program Exercise Date, except as expressly provided otherwise in this Agreement, AstraZeneca is solely responsible for the Development, Manufacture and Commercialization of Products with respect to such Collaboration Target, and will be solely responsible for all costs associated therewith. With respect to each Licensed Program, AstraZeneca will use Commercially Reasonable Efforts (i) to Develop a Product and to seek Approval for such Product for use in humans [***], (ii) following Approval, to Commercialize such Product for use in humans [***], (iii) to Develop and Commercialize a Product for use in humans worldwide (outside of [***]) to the extent consistent with the global commercialization strategy and efforts AstraZeneca would use for AstraZeneca's similar products in the same franchise, and (iv) to Develop and Commercialize each Product substantially in accordance with the applicable IPP.

5.1.1. **Specific Performance Milestone Events**. On a Licensed Program-by-Licensed Program basis, within [***] after the Collaboration Program Exercise Date, AstraZeneca will identify and provide to Isis specific performance milestone events ("***Specific Performance Milestone Events***") for the first Product from such Licensed Program and the [***] based on the information then available to AstraZeneca and its then-current practices, and in all cases consistent with AstraZeneca's then current internal specific performance milestone event metrics for the applicable AstraZeneca franchise. AstraZeneca shall consider in good faith and will not unreasonably refuse to incorporate any proposals and comments made by Isis in connection with such Specific Performance Milestone Events and [***] and once the Specific Performance Milestone Events and [***] are set by AstraZeneca for a given Product, such Specific Performance Milestone Events and [***] will be attached hereto and made a part hereof as SCHEDULE 5.1.1. AstraZeneca will use Commercially Reasonable Efforts to achieve the Specific Performance Milestone events. If regulatory or Development issues arise that impede commencement of activities as anticipated, AstraZeneca will notify Isis and if requested by Isis meet to discuss such delays.

5.1.2. **Integrated Product Plans**. For each Licensed Program, AstraZeneca will prepare a global integrated Product plan or a comparable document consistent with AstraZeneca's then current internal practices for AstraZeneca's internal programs outlining key aspects of the Development of the Product being Developed from such Program as well as, as Development proceeds, and such information is available, key aspects of worldwide regulatory strategy, pricing and market access strategy, market launch, and Commercialization (each plan or other such document, an "***Integrated Product Plan***" or "***IPP***"). AstraZeneca will prepare each IPP no later than [***] for the relevant Product, and the IPP will contain high level information consistent with AstraZeneca's development and commercialization plans for its similar products at similar stages of development and commercialization in the same AstraZeneca franchise. Once AstraZeneca has prepared an IPP, AstraZeneca will update it consistent with AstraZeneca's standard practice (including if the IPP is updated and presented to an AstraZeneca internal committee) but at least Annually and will provide such updates to Isis. AstraZeneca and Isis will meet (through the JSC or as the Parties may otherwise agree) on an Annual basis to discuss the draft of the IPP and AstraZeneca will consider, in good faith, any proposals and comments made by Isis for incorporation in the IPP.

5.1.3. **Investigator's Brochure**. Subject to Section 5.2, AstraZeneca will keep Isis reasonably informed with respect to the status, activities and progress of Development of Products licensed by AstraZeneca hereunder and will provide updated versions of the Investigator's Brochure when requested by Isis (but no more frequently than Annually) or when Development of the Products results in any substantive change to the safety or risk to the Products.

5.2. **Isis Competitive Product**. Notwithstanding Section 2.1, Section 2.3.2, Section 5.1.2, Section 5.1.3, and Section 5.3, on a Product-by-Product basis, if Isis independently or with an Affiliate or Third Party (i) commences a [***] for any product (and has not ceased all development of such product) for the same Indication as AstraZeneca is Developing or Commercializing a Product, or (ii) commercializes any product for the same Indication as AstraZeneca is Developing or Commercializing a Product, then AstraZeneca may at its discretion, following written notice to Isis, cease to provide, or reduce the information, communications, reports or plans provided to Isis pursuant to this Agreement for the affected Product; and unless otherwise agreed by AstraZeneca, Isis will [***], for such affected Product; *provided, however*, that AstraZeneca will continue to (v) provide Isis the information described under Section 5.4 for the Isis Internal ASO Safety Database, (w) provide Isis the royalty reports to be delivered in accordance with Section 6.9, (x) provide Isis with advance notice under Section 11.5 of any material announcements regarding such Product, (y) deliver to Isis on an Annual basis a high-level summary of the IPP for such Product, and (z) meet with Isis through the JSC (or, if the JSC does not exist, with Isis) in accordance with Section 2.1 for Collaboration Programs that do not involve such Product.

5.3. **Regulatory Interactions**.

5.3.1. **Participation in Regulatory Meetings**. Each Party will provide the other Party with as much advance written notice as practicable of any meetings such Party has or plans to have with a Regulatory Authority regarding pre-approval or Approval matters for a Product (or, in the case of Isis as the invitee, that relate to Isis' antisense oligonucleotide platform), and, subject to Section 5.2, will allow one representative of the invited Party to participate (as an observer) in any such meeting that is [***] (e.g., meetings regarding [***]). The costs associated with such observer attendance will be met by the invitee Party, except if Isis' presence has been specifically requested by AstraZeneca, in which case AstraZeneca will reimburse Isis for its time incurred in attending at the FTE Rate. To the extent that AstraZeneca has not fully used the [***] available to it pursuant to Section 4.8.1 or Section 5.3.3, then AstraZeneca will be entitled to allocate such [***] to the activities to be performed by Isis pursuant to this Section 5.3.1.

5.3.2. **Regulatory Communications**. Subject to Section 5.2, each Party will provide the other Party with copies of documents and communications submitted to (including such drafts as the providing Party considers reasonably practicable but to include at least one pre-finalization draft thereof) and received from Regulatory Authorities that materially impact the Development or Commercialization of Products for the other Party's review and comment, and the submitting Party will consider in good faith including any comments provided by the reviewing Party to such documents and communications.

5.3.3. **Assistance with Regulatory Filings**. On a Collaboration Target-by-Collaboration Target basis, after the Collaboration Program Exercise Date, upon AstraZeneca's written request [***], Isis will prepare the reports pertaining to Isis Conducted Activities as required for inclusion in INDs for the Product. AstraZeneca and Isis will co-ordinate to ensure that the content of such reports is suitable for submission to the applicable Regulatory Authorities using AstraZeneca's then-current template for products in the same franchise; *so long as* Isis is able to use such template without incurring more than [***]. If use of such template would require Isis to incur such costs (e.g. in connection with the purchase of software), the Parties shall discuss and agree on the appropriate format for such reports. In addition, Isis will assist AstraZeneca in preparing regulatory filings for the Products (including INDs and other regulatory filings) and, except with respect to regulatory filing-related activities outlined in Section 5.3.1 and Section 5.3.2, such additional regulatory filings assistance will be [***]. Thereafter, upon AstraZeneca's written request, Isis will provide such additional assistance in preparing such regulatory filings for the Products at the FTE Rate, and any of Isis' reasonable travel expenses for travel requested by AstraZeneca, and any of its outside consultants' costs and consultants' reasonable travel expenses incurred by Isis agreed in advance by AstraZeneca. An estimate of such costs and expenses will be provided to AstraZeneca before initiation of agreed work.

5.3.4. **Class Generic Claims**. To the extent AstraZeneca intends to make any claims in a Product label or regulatory filing that are class generic to ASOs or any of Isis' technology incorporated into a Product, AstraZeneca will provide such claims and regulatory filings to Isis in advance and will consider in good faith any proposals and comments made by Isis.

5.3.5. **Applicable Laws**. Each of Isis and AstraZeneca 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.

5.4. Isis' Antisense Safety Database.

5.4.1. 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***"), *provided that* AstraZeneca's obligations pursuant to this Section 5.4.1 are subject to Applicable Laws and in particular AstraZeneca will not be required to disclose any information in contravention of Applicable Laws relating to data privacy. In an effort to maximize understanding of the safety profile and pharmacokinetics of Isis compounds, AstraZeneca will cooperate in connection with populating the Isis Internal ASO Safety Database. To the extent collected by AstraZeneca and, in the form in which AstraZeneca uses/stores such information for its own purposes, AstraZeneca will provide Isis with material information concerning toxicology, pharmacokinetics, safety pharmacology study(ies), serious adverse events and other safety information related to Products licensed by AstraZeneca under this Agreement as soon as practicable following the date such information is available to AstraZeneca (but not later than [***] after AstraZeneca's receipt of such information). In connection with any reported serious adverse event, AstraZeneca will provide Isis all serious adverse event reports, including initial, interim, follow-up, amended, and final reports. In addition, with respect to Products, AstraZeneca will provide Isis with copies of Annual safety updates filed with each IND and the safety sections of any final Clinical Study reports. Furthermore, AstraZeneca will promptly provide Isis with any supporting data and answer any follow-up questions reasonably requested by Isis to conduct analyses to keep Isis and its partners informed regarding class generic properties of ASOs, including with respect to safety. All such information disclosed by AstraZeneca to Isis will be AstraZeneca Confidential Information; *provided*, *however*, that so long as Isis does not disclose the identity of a Product (or the relevant Target) or AstraZeneca's identity, Isis may disclose any such AstraZeneca Confidential Information to Regulatory Authorities and Isis' other partners pursuant to Section 5.4.2 below if such information is regarding class generic properties of ASOs and, with respect to Isis' partners, such partners have agreed to a similar provision permitting the disclosure of their Confidential Information relating to ASOs to Isis' partners. AstraZeneca 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). AstraZeneca will also cause its Affiliates and Sublicensees to comply with this Section 5.4.1.

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

5.5. Manufacturing and Supply.

5.5.1. Initial Supply to AstraZeneca.

(a) With respect to the [***] Licensed Programs, in support of AstraZeneca's further Development of Products to such Collaboration Targets, upon AstraZeneca's written request at least [***] in advance of the requested delivery date, Isis will manufacture and supply up to [***] of API for a Product from each such Licensed Program. If requested by AstraZeneca, Isis will use reasonable endeavors to manufacture and supply API on less than [***] notice to the extent Isis has available capacity.

(b) AstraZeneca will pay Isis for such API at [***], within [***] after AstraZeneca's receipt of the applicable invoice. Subject to Section 5.5.1(c), any request from AstraZeneca for Isis to manufacture API under this Section 5.5.1 will be submitted to Isis within [***] after AstraZeneca's exercise of its Collaboration Program License Right for the applicable Product under this Agreement.

(c) AstraZeneca may place orders for API pursuant to Section 5.5.1(a) prior to exercise of its Collaboration Program License Right for a given Collaboration Target but Isis will not be required to deliver the API until after such exercise. In such circumstances, Isis may invoice AstraZeneca for [***] for such API when such order is placed and the balance [***] on delivery; *provided that* (a) if AstraZeneca does not exercise its Collaboration Program License Right for such Collaboration Target, AstraZeneca shall not be required to [***]; and (b) if Isis continues development of the relevant Product, Isis shall [***].

(d) After AstraZeneca's exercise of its Collaboration Program License Right for the applicable Product under this Agreement, in addition to the supply set forth in this Section 5.5, Isis will sell to AstraZeneca, if AstraZeneca desires, any other inventory of cGMP API and finished drug Product in Isis' possession at [***].

5.5.2. **Manufacturing Services Agreement**. Each of the Parties agrees and acknowledges that a mutually agreed manufacturing services agreement ("***MSA***") is required to be put in place to govern the supply arrangements by Isis under Section 5.5.1, which will be negotiated in good faith between the Parties following the Effective Date and will be in a form substantially similar to that certain Manufacturing and Services Agreement between Isis and AstraZeneca dated March 7, 2013. The Parties' objective is that the MSA will be entered into within [***] after the Effective Date.

5.5.3. AstraZeneca is responsible for supplying finished drug Product for AstraZeneca's Research, Development and Commercialization of Products under this Agreement, and API for the sixth and each subsequent Licensed Program.

ARTICLE 6.
FINANCIAL PROVISIONS

6.1. **Up-Front Fee**. Within 15 days following the Effective Date, AstraZeneca will pay Isis an up-front fee of US$65,000,000 allocated as follows:

6.1.1. $[***] in consideration for the exclusive license granted under Section 4.1.1 to AstraZeneca for [***] Products; and

6.1.2. $[***] in consideration for (i) [***], (ii) [***], and (iii) [***].

6.2. **Product License Fees**. On a Collaboration Program License Right-by-Collaboration Program License Right basis (for Collaboration Programs that are not the [***] Program), following AstraZeneca's written notice to Isis stating that AstraZeneca is exercising such Collaboration Program License Right in accordance with this Agreement, AstraZeneca will pay Isis a license fee of:

6.2.1. For each of the [***] such Collaboration Programs, $[***] within [***] after AstraZeneca's receipt from Isis of an invoice for such license fee; and

6.2.2. For the [***] and each subsequent Collaboration Program, $[***] within [***] after AstraZeneca's receipt from Isis of an invoice for such license fee.

6.3. **[***] Candidate Drug Designation Milestone.** Following AstraZeneca's written notice to Isis stating that AstraZeneca is exercising its Collaboration Program License Right with respect to [***] in accordance with this Agreement, AstraZeneca will pay Isis a milestone payment of $[***] (the "**[***] *CD Milestone***") within [***] after AstraZeneca's receipt from Isis of an invoice for such milestone payment.

6.4. **Milestone Payments for Achievement of Milestone Events by a Product**. On a Licensed Program-by-Licensed Program basis, in accordance with Section 6.5.5, AstraZeneca will pay to Isis the milestone payments as set forth in TABLE 1 below when a milestone event listed in TABLE 1 is first achieved by AstraZeneca, its Affiliates or Sublicensees with respect to a Product under such Licensed Program:

TABLE 1

Product Milestone Event	Product Milestone Event Payment
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]

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

6.5.1. Each milestone payment set forth in TABLE 1 above will be paid only once per Licensed Program upon the first achievement of the milestone event regardless of how many Products for such Licensed Program achieve such milestone event.

6.5.2. If the [***] is a [***], the milestone otherwise payable on "[***]" will not be payable unless and until [***].

6.5.3. If a particular milestone event is not achieved because Development or Commercial 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, each of the "[***]," "[***]" and "[***]" milestone event payments are due. As an additional example, if, after achieving the "[***]" milestone event [***], then 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.

6.5.4. In addition, if a particular milestone event is achieved contemporaneously or in connection with another milestone event, then upon achievement of one such milestone event the other milestone event will also be deemed achieved and the milestone payments for both milestone events are due. For example, if AstraZeneca achieves the "[***]" milestone event and the [***] ([***]) that was the subject of such milestone event [***], then both the "[***]" and the "[***]" milestone event payments are due. Similarly, if AstraZeneca achieves the "[***]" milestone event and the [***] ([***]) that was the subject of such milestone event [***], then both the "[***]" and the "[***]" milestone event payments are due.

6.5.5. Each time a milestone event is achieved under this ARTICLE 6, AstraZeneca will send Isis a written notice thereof promptly (but no later than ten Business Days) following the date of achievement of such milestone event. Thereafter, Isis will promptly invoice AstraZeneca for the achievement of any milestone event under this ARTICLE 6 and such milestone payment will be due within [***] after AstraZeneca's receipt of such invoice.

6.6. [***].

6.6.1. [***]

6.6.2. [***]

6.6.3. ***Examples of*** [***] ***under Section 6.6.2***

6.6.4. [***]

6.7. Royalty Payments to Isis.

6.7.1. **AstraZeneca Full Royalty**. On a Licensed Program-by-Licensed Program basis, as partial consideration for the rights granted to AstraZeneca hereunder, subject to the provisions of this Section 6.7.1 and Section 6.7.2, AstraZeneca will pay to Isis royalties on Annual worldwide Net Sales of Products sold by AstraZeneca, its Affiliates or Sublicensees, on a country-by-country and Product-by-Product basis, in each case in the amounts as follows in TABLE 2 below (the "***AstraZeneca Full Royalty***"):

TABLE 2

Royalty Tier	Annual Worldwide Net Sales of Products from a Licensed 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 ≥ $[***]	[***]%

Subject to Section 6.7.2(d), annual worldwide Net Sales will be calculated by taking the aggregate sum of Net Sales of Products (under the applicable Licensed Program) for all countries worldwide.

(a) During the Royalty Period, AstraZeneca will pay Isis royalties on Net Sales of Products arising from named patient and other similar programs under Applicable Laws, and AstraZeneca will provide reports and payments to Isis consistent with Section 6.9. No royalties are due on Net Sales of Products arising from compassionate use and other programs providing for the delivery of Product at no cost. The sales of Products arising from named patient, compassionate use, or other similar programs will not be considered a First Commercial Sale for purposes of calculating the Royalty Period or determining whether an Approval milestone event listed in TABLE 1 of Section 6.4 has been achieved.

(b) For purposes of clarification, any Isis Product-Specific Patents assigned to AstraZeneca 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.

6.7.2. **Application of Royalty Rates**. All royalties set forth under Section 6.7.1 are subject to the provisions of this Section 6.7.2, and are payable as follows:

(a) **Royalty Period**. AstraZeneca's obligation to pay Isis the AstraZeneca Full Royalty above with respect to a Product will continue on a country-by-country and Product-by-Product basis from the date of First Commercial Sale of such Product until the later of the date of expiration of (i) the last Valid Claim within the Licensed Patents Covering such Product in the country in which such Product is made, used or sold, (ii) the data exclusivity period conferred by the applicable Regulatory Authority in such country with respect to such Product (e.g., such as in the case of an orphan drug), and (iii) the [***] ([***]) anniversary of the First Commercial Sale of the first Product to contain the relevant Compound in such country (such royalty period, the "***Royalty Period***"); *provided*, if, following such [***] ([***]) anniversary of such First Commercial Sale, the only remaining Valid Claim of a Licensed Patent Covering such Product in a country where such Product is made or sold is an Isis Manufacturing and Analytical Patent, then AstraZeneca will pay Isis a reduced royalty for such Product in such country at royalty rates equal to [***] until such Isis Manufacturing and Analytical Patent expires.

(b) **Allocation of Reduction**. The Parties acknowledge that the applicable royalty rate in TABLE 2 is dependent on Annual worldwide Net Sales of Products and any royalty rate reduction in the proviso of Section 6.7.2(a) applies on a country-by-country and Product-by-Product basis. The Parties will apply appropriate mechanisms to apportion any such reduction proportionally across the royalty tiers in TABLE 2.

(c) **Limitation on Aggregate Reduction for AstraZeneca Royalties**.

(i) If the offset under Section 6.7.2(a) does not apply, in no event will the aggregate royalty offsets under Section 6.8.3(b) and Section 6.8.4(b) reduce the royalties payable to Isis on Net Sales of a Product in any given period to an amount that is less than the greater of (A) [***], and (B) [***].

(ii) If the offset under Section 6.7.2(a) applies, in no event will the aggregate royalty offsets under Section 6.7.2(a), Section 6.8.3(b) and Section 6.8.4(b) reduce the royalties payable to Isis on Net Sales of a Product in any given period to an amount that is less than [***].

(d) **End of Royalty Obligation**. On a country-by-country and Product-by-Product basis, other than [***], AstraZeneca's obligation to make royalty payments hereunder in such country will end on the expiration of the Royalty Period in such country. Any sales of a Product made after the expiration of the Royalty Period for such Product in a country shall not be included in the Annual worldwide Net Sales for the purposes of calculating royalties under Section 6.7.1.

(e) **Compulsory Licenses**. If a court or a governmental agency of competent jurisdiction requires AstraZeneca or any of its Affiliates or Sublicensees to grant a compulsory license to a Third Party (each, a "***Compulsory Sublicensee***") permitting such Third Party to make and sell a Product in a country, (i) such Compulsory Sublicensee will not be considered a Sublicensee for the purpose of this Agreement, and (ii) such grant will be permitted and deemed consented to by Isis under Section 4.1.2. At such time as AstraZeneca or any of its Affiliates or Sublicensees enters into a sublicense with a Compulsory Sublicensee, [***]; *provided that* [***].

6.8. **Third Party Payment Obligations that are Not Relevant to New Third Party Compound Technology**. Any Third Party Obligations that become payable by Isis or AstraZeneca under an agreement such Party has entered into to license or otherwise acquire Third Party Patent Rights or other intellectual property rights, in each case that are not New Third Party Compound Technology will be paid by a Party or shared by the Parties as expressly set forth in this Section 6.8:

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

(a) ***Isis' Existing Technology In-License Agreements***. Certain of the Licensed Technology that may be licensed to AstraZeneca under Section 4.1.1 is in-licensed or was acquired by Isis under the agreements with Third Party licensors or sellers listed in APPENDIX 3, 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 or Commercialization of a Product by AstraZeneca, its Affiliate or Sublicensee under this Agreement. Any such payment obligations arising under the Isis In-License Agreements listed on APPENDIX 3 to the extent not applicable to New Third Party Compound Technology:

(i) as they apply to (x) any Patent Right or Know-How claiming [***], or (y) [***], in each case licensed by Isis to AstraZeneca in connection with the applicable Product, will be paid by [***] as [***], and

(ii) as they apply to [***] and [***], in each case licensed by Isis to AstraZeneca in connection with the applicable Product, will be paid by [***] as [***].

(b) ***AstraZeneca's Existing In-License Agreements***. AstraZeneca will be solely responsible for any Third Party Obligations that become payable by AstraZeneca to Third Parties under any agreements or arrangements AstraZeneca has with such Third Parties as of the Effective Date, based on the Development or Commercialization of a Product by AstraZeneca, its Affiliate or Sublicensee under this Agreement. Any such payment obligations will be paid by AstraZeneca as AstraZeneca Supported Pass-Through Costs under this Agreement.

6.8.2. New In-Licensed Additional Product-Specific Patents.

(a) **Prior to Exercise of a Collaboration Program License Right**. On a Collaboration Target-by-Collaboration Target basis, if, prior to AstraZeneca's exercise of its Collaboration Program License Right, Isis obtains Third Party Patent Rights necessary to Develop or Commercialize a Product where such Patent Right would have satisfied the definition of an Isis Product-Specific Patent had Isis Controlled such Patent Rights on the Effective Date, then to the extent Controlled by Isis, Isis will include such Third Party Patent Rights in the license to be granted to AstraZeneca under Section 4.1.1 if [***]. Isis will consult with AstraZeneca before entering into such Third Party agreement and will take into consideration any reasonable comments made by AstraZeneca. On such agreement by AstraZeneca, such in-license agreement shall be an Isis In-License Agreement and APPENDIX 3 shall be updated accordingly.

(b) **After Exercise of Collaboration Program License Right**.

(1) On a Collaboration Target-by-Collaboration Target basis, after AstraZeneca exercises its Collaboration Program License Right, AstraZeneca or Isis, as the case may be, will promptly provide the other Party written notice of any additional Third Party Patent Rights necessary to practice an Isis Product-Specific Patent to Develop or Commercialize a Product ("***Additional Product-Specific Patents***") it believes it has identified and AstraZeneca will have the first right, but not the obligation, to negotiate with, and obtain a license from the Third Party Controlling such Additional Product-Specific Patents. If AstraZeneca obtains any such Additional Product-Specific Patents then any and all Third Party Obligations arising under such Third Party agreement will be paid by [***] as [***].

(2) If, however, AstraZeneca elects not to obtain such a license to such Additional Product-Specific Patents, AstraZeneca will so notify Isis, and Isis may obtain such a license to such Additional Product-Specific Patents and will include such Additional Product-Specific Patents in the license granted to AstraZeneca under Section 4.1.1 [***]. On such agreement by AstraZeneca, such in-license agreement shall be an Isis In-License Agreement and APPENDIX 3 shall be updated accordingly.

6.8.3. Additional Core IP In-License Agreements.

(a) AstraZeneca will promptly provide Isis written notice of any intellectual property controlled by a Third Party that is necessary to [***] that *is not* New Third Party Compound Technology ("***Additional Core IP***") that AstraZeneca 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. For clarity, Additional Core IP does not include any Patent Rights claiming (or intellectual property related to) [***] or New Third Party Compound Technology. If Isis obtains such a Third Party license, Isis will include such Additional Core IP in the license granted to AstraZeneca under Section 4.1.1, and [***] will pay any financial obligations under such Third Party agreement as [***]. Provided that AstraZeneca has agreed the terms of such agreement, such agreement shall be an Isis In-License Agreement and APPENDIX 3 shall be updated accordingly.

(b) If, however, Isis elects not to obtain such a license to such Additional Core IP, Isis will so notify AstraZeneca, and AstraZeneca may obtain such a Third Party license and AstraZeneca may offset an amount equal to [***] against [***].

6.8.4. Disputes Regarding Additional Core IP.

(a) If Isis does not agree that certain intellectual property identified by AstraZeneca pursuant to Section 6.8.3(a) is Additional Core IP, Isis will send written notice to such effect to AstraZeneca, 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 [***]. The costs of any Third Party expert engaged under this Section 6.8.4 will be paid by the Party against whose position the Third Party lawyer's determination is made.

(b) Notwithstanding the determination of the Third Party lawyer under Section 6.8.4(a), if a Third Party Controlling Additional Core IP is awarded a judgment from a court of competent jurisdiction arising from its claim against AstraZeneca asserting that [***], AstraZeneca will be permitted to (i) [***] and (ii) [***].

6.8.5. **Isis In-License Agreements**. The Isis In-License Agreements in existence at the Execution Date are listed in APPENDIX 3. After the Effective Date APPENDIX 3 will be updated in accordance with Section 1.13.2, Section 6.8.2(a), Section 6.8.2(b)(2), Section 6.8.3(a), Section 6.9, and Section 8.4.2. Any such update will on a Collaboration Target-by-Collaboration Target basis, identify the relevant intellectual property rights, any AstraZeneca Supported Pass Through Costs and any Isis Supported Pass Through Costs.

6.8.6. ***Minimum Third Party Payments***. Any Minimum Third Party Payments AstraZeneca is obligated to pay under this Agreement will be satisfied by [***].

6.9. New Third Party Compound Technology.

6.9.1. **Existing New Third Party Compound Technology**. Where AstraZeneca agrees to incorporate New Third Party Compound Technology into an ASO under the Drug Discovery Plan in accordance with Section 1.13.2, Isis will include such technology in the license granted to AstraZeneca under Section 4.1.1 and, subject to Section 6.9.3, [***] will pay [***] to the extent triggered by the Manufacturing, Development or Commercialization of a Product by Isis in the conduct of the Drug Discovery Plan or by or on behalf of AstraZeneca.

6.9.2. **Additional New Third Party Compound Technology**. If, (i) in order to grant a license to AstraZeneca to New Third Party Compound Technology that the Parties agree to incorporate into an ASO in accordance with Section 1.13.2, it is necessary for Isis to obtain a license from the Third Party controlling such New Third Party Compound Technology, or (ii) at any time after the Parties decide to incorporate New Third Party Compound Technology into an ASO pursuant to Section 1.13.2, either Party becomes aware of any intellectual property controlled by a Third Party that is necessary to practice such New Third Party Compound Technology to Develop, Manufacture or Commercialize a Product, then (A) Isis will consult with AstraZeneca before entering into an agreement with such Third Party for access to such New Third Party Compound Technology or such intellectual property necessary to practice such New Third Party Compound Technology, (B) Isis will take into consideration any reasonable comments made by AstraZeneca to such agreement, and (C) to the extent the economic terms of such Third Party agreement are Third Party Obligations that will be paid by [***] as [***], such economic terms will be [***] prior to Isis executing such agreement with such Third Party. On such agreement by [***] to pay such [***] as [***], Isis will include such technology in the license granted to AstraZeneca under Section 4.1.1, such in-license agreement shall be an Isis In-License Agreement, and APPENDIX 3 shall be updated accordingly. If Isis elects not to obtain such a license to New Third Party Compound Technology, Isis will so notify AstraZeneca, and AstraZeneca may obtain such a Third Party license [***].

6.9.3. AstraZeneca will not be responsible for any [***] paid by Isis with respect to New Third Party Compound Technology and if any [***] with respect to New Third Party Compound Technology are triggered prior to exercise of the applicable Collaboration Program Exercise Date, AstraZeneca will not be required to pay such amount unless and until such exercise.

6.10. Payments.

6.10.1. Commencement. Beginning with the Calendar Quarter in which the First Commercial Sale for a Product is made and for each Calendar Quarter thereafter, AstraZeneca will make royalty payments to Isis under this Agreement within [***] following the end of each such Calendar Quarter. Each royalty payment will be accompanied by a report, summarizing Net Sales for Products during the relevant Calendar Quarter and the calculation of royalties due thereon, including country, units, sales price and the exchange rate used. If no royalties are payable in respect of a given Calendar Quarter, AstraZeneca 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, AstraZeneca will provide Isis a preliminary, non-binding Product sales estimate for such Calendar Quarter.

6.10.2. 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 (except as otherwise provided in Section 6.6 or Section 6.11), 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 AstraZeneca in accordance with the rates of exchange for the relevant month for converting such other currency into US Dollars used by AstraZeneca's internal accounting systems, which are independently audited on an annual basis and which are in accordance with generally accepted accounting principles, fairly applied and as employed on a consistent basis throughout AstraZeneca's operations.

6.10.3. Records Retention. Commencing with the First Commercial Sale of a Product, AstraZeneca 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 AstraZeneca hereunder.

6.11. **Audits**. During the Agreement Term and for a period of [***] thereafter, at the request and expense of Isis, AstraZeneca will permit an independent certified public accountant of nationally recognized standing appointed by Isis and reasonably acceptable to AstraZeneca, at reasonable times and upon reasonable notice, but in no case more than [***] per Calendar Year, to examine such records as may be necessary for the purpose of verifying the accrual of any milestone payments, the calculation and reporting of Net Sales, the correctness of any milestone or royalty payment made under this Agreement, and any calculation contemplated by Section 6.7.2(e) for any period within the preceding [***]. As a condition to examining any records of AstraZeneca, such auditor will sign a nondisclosure agreement reasonably acceptable to AstraZeneca in form and substance. Any and all records of AstraZeneca examined by such independent certified public accountant will be deemed AstraZeneca's Confidential Information. Upon completion of the audit, the accounting firm will provide both AstraZeneca and Isis with a written report disclosing whether the milestone or royalty payments and any calculation contemplated by Section 6.7.2(e) made by AstraZeneca 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 AstraZeneca, it is shown that AstraZeneca's payments under this Agreement were more or less than the milestone or royalty amount which should have been paid, then the relevant Party will make all payments required to be made by paying the other Party the difference between such amounts to eliminate any discrepancy revealed by said inspection within 45 days of receiving the Audit Report, with interest calculated in accordance with Section 6.13; *provided, however*, that any such payment by Isis to AstraZeneca will be [***]. Isis will pay for such audit, except that if AstraZeneca is found to have underpaid Isis by more than [***]% of the amount that should have been paid for the audited period, AstraZeneca will reimburse Isis the reasonable fees and expenses charged by the accounting firm for the audit.

6.12. **Taxes**.

6.12.1. **Taxes On Income**. Each Party alone will be solely responsible for paying any and all Taxes (other than withholding taxes required by Applicable Law to be paid by AstraZeneca or Isis (as the case may be) levied on account of, or measured in whole or in part by reference to, the income of such Party.

6.12.2. **Indirect Taxes**. All payments are exclusive of Indirect Taxes. If any Indirect Taxes are chargeable in respect of any payments, the paying Party will pay such Indirect Taxes at the applicable rate in respect of such payments following receipt, where applicable, of an Indirect Taxes invoice in the appropriate form issued by the receiving Party in respect of those payments.

The Parties will issue invoices for all amounts payable under this Agreement consistent with Indirect Tax requirements and irrespective of whether the sums may be netted for settlement purposes. If such amounts of Indirect Taxes are refunded by the applicable Governmental Authority or other fiscal authority subsequent to payment, the Party receiving such refund will transfer such amount to the paying Party within 45 days of receipt. The Parties agree to reasonably cooperate to provide any information required by the Party pursuing a refund of Indirect Taxes paid.

6.12.3. **Withholding Tax**. To the extent the paying Party is required to deduct and withhold taxes on any payment, the paying Party will pay the amounts of such taxes to the proper governmental authority for the account of the receiving Party and remit the net amount to the receiving Party in a timely manner. The paying Party will promptly furnish the receiving Party with proof of payment of such taxes. If documentation is necessary in order to secure an exemption from, or a reduction in, any withholding taxes, the Parties will provide such documentation to the extent they are entitled to do so. In accordance with the procedures set forth in Section 9.3 and Section 9.4, (i) the receiving Party will also indemnify the paying Party for any tax, interest or penalties imposed on the paying Party if the paying Party improperly reduces or eliminates withholding tax based upon representations made by the receiving Party, and (ii) Isis will indemnify AstraZeneca for any withholding tax incurred on AstraZeneca Supported Pass-Through Costs paid by AstraZeneca to Isis that arises because these costs are deemed to not be beneficially owned by Isis.

6.12.4. **Tax Cooperation**. At least 15 days prior to the date a given payment is due under this Agreement, the non-paying Party will provide the paying Party with any and all tax forms that may be reasonably necessary in order for the paying Party to lawfully not withhold tax or to withhold tax at a reduced rate with respect to such payment under an applicable bilateral income tax treaty. Following the paying Party's timely receipt of such tax forms from the non-paying Party, the paying Party 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. The non-paying Party will provide any such tax forms to the paying Party upon request and in advance of the due date. Each Party will provide the other with reasonable assistance to enable the recovery, as permitted by Applicable Law, of withholding taxes resulting from payments made under this Agreement, such recovery to be for the benefit of the Party who would have been entitled to receive the money but for the application of withholding tax under this Section 6.12.

The provisions of this Section 6.12 are to be read in conjunction with the provisions of Section 12.3 below.

6.13. **Interest**. Any undisputed payments to be made hereunder that are not paid on or before the date such payments are due under this Agreement, and any payments that are pending resolution of any dispute unless the dispute is ruled in favor of the paying Party, 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 AstraZeneca 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 AstraZeneca will own and retain all of its rights, title and interest in and to the AstraZeneca Background Intellectual Property, AstraZeneca Know-How and AstraZeneca Patents, subject to any assignments, rights or licenses expressly granted by one Party to the other Party under this Agreement. For clarity, except as otherwise expressly provided in this Agreement, the scope of licenses granted by AstraZeneca under this Agreement will not include AstraZeneca Background Intellectual Property.

7.1.2. Collaboration Technology. As between the Parties, each Party shall own and retain all right, title and interest in and to any and all Know-How that is conceived, discovered, developed or otherwise made by or on behalf of such Party (or its Affiliates) under or in connection with this Agreement, whether or not patented or patentable and any and all Patent Rights and other intellectual property rights with respect thereto.

7.1.3. Disclosure of Collaboration Technology.

(a) AstraZeneca will promptly disclose to Isis, and will cause its Affiliates to so disclose, the discovery, development, or creation of any AstraZeneca Collaboration Intellectual Property.

(b) Isis will promptly disclose to AstraZeneca, and will cause its Affiliates to so disclose, the discovery, development, or creation of any Isis Collaboration Intellectual Property.

7.1.4. Jointly Owned Collaboration Technology. The Parties shall each own an equal, undivided interest in any and all such Know-How and Patent Rights that are conceived, discovered, developed or otherwise made jointly by or on behalf of the Parties under or in connection with this Agreement. Inventorship will be determined in accordance with Section 7.1.5(b). Each Party shall, without additional compensation, cooperate to make any necessary assignments to fully effect the ownership provided for in this Section 7.1.4. Except as expressly provided in this Agreement, without limiting the exclusive licenses granted under Section 4.1.1 or the exclusivity covenants under Section 3.1, 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 Collaboration Technology by reason of joint ownership thereof, and each Party hereby waives any right it may have under the laws of any jurisdiction to require any such consent or accounting; *provided that* [***].

7.1.5. IP Managers.

(a) Each Party will appoint one of its in-house patent attorneys to serve as the primary contact with respect to intellectual property matters arising under this Agreement (the "***IP Managers***") and will cooperate with respect to the activities set forth in this ARTICLE 7. A strategy will be discussed with regard to (x) prosecution and maintenance, defense and enforcement of Isis Product-Specific Patents, AstraZeneca Product-Specific Patents and Jointly-Owned Collaboration Patents that would be or are licensed to AstraZeneca under Section 4.1.1, (y) defense against allegations of infringement of Third Party Patent Rights, and (z) 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 this Agreement or the licenses granted hereunder. In addition, the IP Managers will ensure that all Patent Rights claiming (i) the specific composition of matter (the exact sequence and chemistry) of a prospective or designated Lead Candidate or Development Candidate, and/or (ii) methods of using such Compound as a prophylactic, therapeutic or diagnostic, will be separated into their own patent applications separate from other subject matter to ensure any such claims are initially licensed to AstraZeneca under Section 4.1.1 and then assigned as Isis Product Specific Patents under Section 4.2.1.

(b) In addition, the IP Managers will be responsible for the determination of inventorship. The determination of inventorship will be made in accordance with United States patent laws and therefore this will determine if the invention is solely or jointly owned by the relevant Party or Parties. To the extent reasonably requested by either Party, the IP Managers 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 Senior Representatives for input and resolution pursuant to Section 12.1.1. Each Party's IP Mangers 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 or Section 7.2.3 will endeavor to obtain patent protection for the Product as it Prosecutes and Maintains its other patents Covering products in development, using counsel of its own choice (but with respect to Patent Rights licensed to AstraZeneca under Section 4.1.1, counsel reasonably acceptable to AstraZeneca), in such countries as the responsible Party sees fit.

7.2.2. Licensed Patents and AstraZeneca Patents.

(a) **Isis Core Technology Patents and Isis Manufacturing and Analytical Patents**. 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) **Isis Product-Specific Patents and Jointly-Owned Collaboration Patents**. On a Collaboration Target-by-Collaboration Target basis, following the Collaboration Program Exercise Date (so long as the applicable license to AstraZeneca under Section 4.1.1 is in effect), AstraZeneca will control and be responsible for all aspects of the Prosecution and Maintenance of the (i) Isis Product-Specific Patents and (ii) Jointly-Owned Collaboration Patents that are not Isis Core Technology Patents or Isis Manufacturing and Analytical Patents, in each case (i) and (ii) to the same extent Isis had the right to control and was responsible for such Prosecution and Maintenance immediately prior to such license (or such milestone payment), subject to Section 7.2.3.

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

7.2.3. Jointly-Owned Collaboration Patents. Isis will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Collaboration Patents (i) that are Isis Core Technology Patents or Isis Manufacturing and Analytical Patents, (ii) that do not Cover Products, and (iii) for Collaboration Targets prior to the applicable Collaboration Program Exercise Date. AstraZeneca will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Collaboration Patents licensed to AstraZeneca under Section 4.1.1 (and with respect to [***], following the Collaboration Program Exercise Date) that Cover Products and are not Isis Core Technology Patents or Isis Manufacturing and Analytical Patents.

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

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

(b) If AstraZeneca elects (i) not to file and prosecute patent applications for the Jointly-Owned Collaboration Patents or Isis Product-Specific Patents that have been licensed or assigned to AstraZeneca under this Agreement or the AstraZeneca Product-Specific Patents ("***AstraZeneca-Prosecuted Patents***") in a particular country, (ii) not to continue the prosecution (including any interferences, oppositions, reissue proceedings, re-examinations, and patent term extensions, adjustments, and restorations) or maintenance of any AstraZeneca-Prosecuted Patent in a particular country, or (iii) not to file and prosecute patent applications for the AstraZeneca-Prosecuted Patent in a particular country following a written request from Isis to file and prosecute in such country, then AstraZeneca 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 Isis will have the right, but not the obligation, to file, prosecute, maintain, enforce, or otherwise pursue such AstraZeneca-Prosecuted Patent in the applicable country at its own expense with counsel of its own choice. In such case, AstraZeneca will cooperate with Isis to file for, or continue to Prosecute and Maintain or enforce, or otherwise pursue such AstraZeneca-Prosecuted Patent in such country in Isis' own name, but only to the extent that AstraZeneca is not required to take any position with respect to such abandoned AstraZeneca-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 AstraZeneca under this Agreement. Notwithstanding anything to the contrary in this Agreement, if Isis assumes responsibility for the Prosecution and Maintenance of any such AstraZeneca-Prosecuted Patent under this Section 7.2.4(b), Isis will have no obligation to notify AstraZeneca if Isis intends to abandon such AstraZeneca-Prosecuted Patent.

(c) The Parties, through the IP Managers, will cooperate in good faith to determine if and when any divisional or continuation applications will be filed with respect to any Jointly-Owned Collaboration 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.

(d) If the Party responsible for Prosecution and Maintenance pursuant to Section 7.2.3 intends to abandon such Jointly-Owned Collaboration Patent without first filing a continuation or substitution, then such Party will notify the other Party of such intention at least 60 days before such Jointly-Owned Collaboration 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 Collaboration Patents. If a Party assumes responsibility for the Prosecution and Maintenance of any such Jointly-Owned Collaboration Patents under this Section 7.2.4(d), such Party will have no obligation to notify the other Party of any intention of such Party to abandon such Jointly-Owned Collaboration Patents.

(e) In addition, the Parties will consult, through the IP Managers, 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 Collaboration Patents. Unless the Parties agree otherwise, Isis and AstraZeneca will share equally the Patent Costs associated with the Prosecution and Maintenance of Jointly-Owned Collaboration Patents; *provided that,* either Party may decline to pay its share of costs for filing, prosecuting and maintaining any Jointly-Owned Collaboration 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 Collaboration Patents.

7.3.2. Licensed Patents and AstraZeneca Patents. Except as set forth in Section 7.2.3 and Section 7.3.1, each Party will be responsible for all Patent Costs incurred by such Party prior to and after the Effective Date in all countries in the Prosecution and Maintenance of Patent Rights for which such Party is responsible under Section 7.2.

7.4. Defense of Claims Brought by Third Parties.

7.4.1. **Products – Prior to AstraZeneca Exercising a Collaboration Program License Right**. 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 any Product with respect to which AstraZeneca has not yet exercised its Collaboration Program License Right, Isis will have the first right, but not the obligation, to defend against any such Proceeding at its sole cost and expense. If Isis elects to defend against such Proceeding, then Isis will have the sole right to direct the defense and to elect whether to settle such claim; *provided, however*, Isis will not settle such Proceeding without the prior written consent of AstraZeneca (such consent not to be unreasonably withheld, conditioned or delayed). AstraZeneca will reasonably assist Isis in defending such Proceeding and cooperate in any such litigation at the request and expense of Isis. Isis will provide AstraZeneca with prompt written notice of the commencement of any such Proceeding that is of the type described in this Section 7.4.1, and Isis will keep AstraZeneca apprised of the progress of such Proceeding. If Isis elects not to defend against such a Proceeding, then Isis will so notify AstraZeneca in writing within 60 days after Isis first receives written notice of the initiation of such Proceeding, and AstraZeneca will have the right, but not the obligation, to defend against such Proceeding at its sole cost and expense and thereafter AstraZeneca will have the sole right to direct the defense thereof, including the right to settle such claim (but only with the prior written consent of Isis, which consent will not be unreasonably withheld, delayed or conditioned). 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. **Products After AstraZeneca Exercises a Collaboration Program License Right**. 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 any Product being Developed or Commercialized by AstraZeneca under a license granted under Section 4.1.1, then AstraZeneca will have the first right, but not the obligation, to defend against any such Proceeding at its sole cost and expense. If AstraZeneca elects to defend against such Proceeding, then AstraZeneca 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 Isis, not to be unreasonably withheld, conditioned or delayed). Isis will reasonably assist AstraZeneca in defending such Proceeding and cooperate in any such litigation at the request and expense of AstraZeneca. AstraZeneca will provide Isis with prompt written notice of the commencement of any such Proceeding that is of the type described in this Section 7.4.2, and AstraZeneca will keep Isis apprised of the progress of such Proceeding. If AstraZeneca elects not to defend against a Proceeding, then AstraZeneca will so notify Isis in writing within 60 days after AstraZeneca first receives written notice of the initiation of such Proceeding, and Isis will have the right, but not the obligation, to defend against such a Proceeding at its sole cost and expense and thereafter Isis will have the sole right to direct the defense thereof, including the right to settle such claim (but only with the prior written consent of AstraZeneca, which consent will not be unreasonably withheld, delayed or conditioned). Notwithstanding the foregoing, if [***]; *provided, however*, [***]. 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.

7.4.3. **Discontinued Product**. If a Third Party initiates a Proceeding claiming that any Patent Right or Know-How owned by or licensed to such Third Party is infringed by the Development, Manufacture or Commercialization of a Discontinued Product, Isis will have the first right, but not the obligation, to defend against and settle such Proceeding at its sole cost and expense. AstraZeneca 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 AstraZeneca 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 7.4.3, and Isis will promptly furnish AstraZeneca with a copy of each communication relating to the alleged infringement received by Isis.

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

7.5. **Enforcement of Patents Against Competitive Infringement**. With respect to infringement, unauthorized use, misappropriation or threatened infringement by a Third Party of any Product-Specific Patents by reason of the development, manufacture, use or commercialization of a product that binds to a Collaboration Target in the Field ("***Competitive Infringement***"), prior to the applicable Collaboration Program Exercise Date, Isis will have the sole right (with no obligation to discuss with AstraZeneca), but not the obligation, to institute, prosecute, and control a Proceeding with respect thereto. With respect to any Competitive Infringement after the applicable Collaboration Program Exercise Date, the Parties will handle such Competitive Infringement in accordance with the remainder of this Section 7.5.

7.5.1. **Duty to Notify of Competitive Infringement**. If either Party learns of a Competitive Infringement by a Third Party to which such Party does not owe any obligation of confidentiality, 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 7.5.6 below, such written notice will be given within 10 days.

7.5.2. **Control of Competitive Infringement Proceedings**. For any Competitive Infringement with respect to a Product licensed to AstraZeneca under Section 4.1.1 that occurs after the applicable Collaboration Program Exercise Date, so long as part of such Proceeding AstraZeneca also enforces any Patent Rights Controlled by AstraZeneca (including any Isis Product-Specific Patents assigned by Isis to AstraZeneca under this Agreement) being infringed that Cover such Product, then AstraZeneca 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,* AstraZeneca will have the right to control such litigation. If AstraZeneca 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 AstraZeneca 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 AstraZeneca will have the right to be represented in any such action by counsel of its own choice at its own expense. Notwithstanding the foregoing, if [***]; *provided, however*, [***].

7.5.3. **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 7.5.4, the costs and expenses of each Party incurred pursuant to this Section 7.5.3(a) will be borne by the Party initiating such Proceeding; *provided* AstraZeneca will only be requested to join such a Proceeding if such Proceeding relates to a Patent Right or Product licensed to AstraZeneca under Section 4.1.1.

(b) If one Party initiates a Proceeding in accordance with this Section 7.5.3, 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.

7.5.4. **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 will be allocated as follows: (A) if Isis initiates or controls the defense of the Proceeding pursuant to Section 7.4.1, Section 7.4.2, Section 7.4.3 or Section 7.5.2 [***]; (B) if AstraZeneca initiates or controls the defense of the Proceeding pursuant to Section 7.4.1, AstraZeneca will receive and retain [***]% of the remaining proceeds and Isis will receive and retain [***]% of the remaining proceeds; and (C) if AstraZeneca initiates or controls the defense of the Proceeding pursuant to Section 7.4.2 or 7.5.2, [***].

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

7.5.6. **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 AstraZeneca 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 Collaboration Patents**. With respect to the infringement in the Field of a Jointly-Owned Collaboration 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) (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, [***].

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

7.7. **Patent Listing**.

7.7.1. **AstraZeneca's Obligations**. AstraZeneca will promptly, accurately and completely list, with the applicable Regulatory Authorities during the Agreement Term, all applicable Patent Rights that Cover a Product licensed to AstraZeneca under Section 4.1.1. Prior to such listings, the Parties will meet, through the IP Managers, to evaluate and identify all applicable Patent Rights, and AstraZeneca will have the right to review, where reasonable, original records relating to any invention for which Patent Rights are being considered by the IP Managers for any such listing. Notwithstanding the preceding sentence, AstraZeneca will retain final decision-making authority as to the listing of all applicable Patent Rights for a 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, all applicable Patent Rights that Cover a Discontinued Product. Prior to such listings, the IP Managers will meet 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 IP Managers for any such listing. Notwithstanding the preceding sentence, Isis will retain final decision-making authority as to the listing of all applicable Patent Rights for such Discontinued Products, as applicable, regardless of which Party owns such Patent Rights.

7.8. **Joint Research Agreement under the Leahy-Smith America Invents Act**. If a Party intends to invoke its rights under 35 U.S.C. § 102(c) of the Leahy-Smith America Invents Act, it will notify the other Party and neither Party will make an election under such provision when exercising its rights under this ARTICLE 7 without the prior written consent of the other Party (such consent not to be unreasonably withheld, conditioned or delayed), and the Parties will use reasonable efforts to cooperate and coordinate their activities with such Party 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 35 U.S.C. § 100(h).

7.9. **Obligations to Third Parties**. Notwithstanding any of the foregoing, each Party's rights and obligations with respect to Licensed Technology under this ARTICLE 7 will be subject to the Third Party rights and obligations under any (i) Third Party agreements the restrictions and obligations of which AstraZeneca has agreed to under Section 1.13.2, Section 6.8.2(a) or Section 6.8.2(b)(2), (ii) Prior Agreements as such agreements are in effect on the date such Collaboration Target was designated as a High Interest Target and placed on the High Interest Target List (or, with respect to [***], the Execution Date) (and not as such Prior Agreement may be amended thereafter), and (iii) Isis In-License Agreements as such agreements are in effect on the date identified as Isis In-License Agreements and added to APPENDIX 3 in accordance with Section 6.8.5 and have been disclosed to AstraZeneca prior to such date (and in the form disclosed to AstraZeneca prior to such date and not as such Isis In-License Agreements may be amended thereafter unless such amendment is made with AstraZeneca's prior written consent); *provided*, *however*, that, to the extent that Isis has a non-transferable right to prosecute, maintain or enforce any Patent Rights licensed to AstraZeneca hereunder and this Agreement purports to grant any such rights to AstraZeneca, Isis will act in such regard with respect to such Patent Rights at AstraZeneca's direction.

7.10. **Additional Rights and Exceptions**. Notwithstanding any provision of this ARTICLE 7, but subject to Section 7.4.4, 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 a Product, and AstraZeneca will determine which Isis Product-Specific Patents will be extended. For clarity, with respect to any Isis Product-Specific Patent for which AstraZeneca has an exclusive license under Section 4.1.1, as between AstraZeneca and any Third Party granted a license by Isis outside the Field under any such Isis Product-Specific Patents, AstraZeneca will determine which Isis Product-Specific Patents will be extended.

7.12. **UPC**. With respect to any Isis Product-Specific Patents, AstraZeneca will have the right to determine whether to opt in or opt out (and to opt in again) of the Unified Patent Court system and if requested by AstraZeneca, Isis will promptly do all things reasonably necessary and execute all documents required to give effect to such decision(s), *provided that* [***].

ARTICLE 8.
REPRESENTATIONS AND WARRANTIES

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

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

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

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

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

8.1.5. all employees, consultants, or (sub)contractors (except (i) academic collaborators, (ii) Third Parties under the Permitted Licenses or Prior Agreements and (iii) in relation to AstraZeneca and its Affiliates, any Third Parties appointed on the terms of agreements described in Section 4.1.2(e)); of such Party or Affiliates performing Development activities hereunder on behalf of such Party are, and such Party hereby covenants to the other Party that they will be, obligated to assign all right, title and interest in and to any inventions developed by them, whether or not patentable, to such Party or Affiliate, respectively, as the sole owner thereof;

8.1.6. such Party will, and such Party hereby covenants to the other Party that it will, perform its activities pursuant to this Agreement in compliance with good laboratory and clinical practices and cGMP and Applicable Law, in each case as applicable under the laws and regulations of the country and the state and local government wherein such activities are conducted, and with respect to the care, handling and use in Development activities hereunder of any non-human animals by or on behalf of such Party, will at all times comply (and will ensure compliance by any of its subcontractors) with all applicable national, federal, state and local laws, regulations and ordinances in performing its obligations under this Agreement; and

8.1.7. such Party is not debarred under the United States Federal Food, Drug and Cosmetic Act or comparable Applicable Laws and it does not, and will not during the Agreement Term, employ or use the services of any person or entity who is debarred, in connection with the Development, manufacture or commercialization of the Products. If either Party becomes aware of the debarment or threatened debarment of any person or entity providing services to such Party, including the Party itself and its Affiliates or Sublicensees, which directly or indirectly relate to activities under this Agreement, the other Party will be immediately notified in writing.

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

8.2.1. Isis is the owner of, or otherwise has the right to grant all rights and licenses it purports to grant to AstraZeneca with respect to the Licensed Technology under this Agreement for Compounds identified by Isis on or before the Effective Date or any Collaboration Programs as they exist on the Effective Date;

8.2.2. to Isis' Knowledge, all Licensed Patents have been filed and maintained properly and correctly in all material respects.

8.2.3. Isis has not previously entered into any agreement, whether written or oral, with respect to, or otherwise assigned, transferred, licensed, conveyed or otherwise encumbered its right, title or interest in or to, the Licensed Technology (including by granting any covenant not to sue with respect thereto) in such a way as to make the representation set forth in Section 8.2.1 not true, and it will not enter into any such agreements or grant any such right, title or interest to any Person that is inconsistent with the rights and licenses granted to AstraZeneca under this Agreement;

8.2.4. to Isis' Knowledge, each of the Licensed Patents properly identifies each and every inventor of the claims thereof as determined in accordance with the laws of the jurisdiction in which such Patent Right is issued or such application is pending;

8.2.5. Isis has not received any written claim alleging, and does not have Knowledge of any fact or circumstance indicating, that any of the Licensed Patents are invalid or unenforceable, including any Licensed Patents required in order for Isis to conduct its obligations under the Collaboration Plans as they exist on the Effective Date (or the applicable Bring-Down Date), in each case with respect to the Collaboration Targets, Compounds and Products identified by Isis on or before the Effective Date;

8.2.6. Isis has not received any written claim alleging, and does not have Knowledge of any fact or circumstance indicating, that any of Isis' activities relating to the Collaboration Targets, Compounds and Products identified by Isis on or before the Effective Date infringe any intellectual property rights of a Third Party;

8.2.7. to Isis' Knowledge, (i) the Isis In-License Agreements and the licenses granted to Isis under the Isis In-License Agreements are in full force and effect, (ii) Isis has not received any written notice, and has no Knowledge, of any breach by any party to any Isis In-License Agreement, and (iii) Isis' performance of its obligations under this Agreement (including the Collaboration Plans as they exist on the Effective Date or the applicable Bring-Down Date) will not constitute a breach of Isis' obligations under the Isis In-License Agreements and the licenses granted to Isis thereunder;

8.2.8. to Isis' Knowledge, Isis does not require any additional licenses or other intellectual property rights in order for Isis to conduct its obligations under the Collaboration Plans as they exist on the Effective Date (or the applicable Bring-Down Date), in each case with respect to the Collaboration Targets and Compounds identified by Isis on or before the Effective Date;

8.2.9. to Isis' Knowledge, in respect of the pending United States patent applications included in the Licensed Patents, Isis has submitted all material prior art of which it is aware in accordance with the requirements of the United States Patent and Trademark Office;

8.2.10. to Isis' Knowledge, (i) neither Isis nor its Affiliates owns or Controls any Patent Rights or Know How covering formulation or delivery technology as of the Effective Date and (ii) there are no additional licenses (beyond those that would be granted to AstraZeneca under Section 4.1.1 upon the exercise of the Collaboration Program License Right for a Collaboration Target) under any intellectual property owned or Controlled by Isis or its Affiliates as of the Effective Date, in each case (i) and (ii) that would be necessary or useful in order for AstraZeneca to further Develop, Manufacture or Commercialize Compounds contemplated under the Collaboration Plans as they exist on the Effective Date (or the applicable Bring-Down Date);

8.2.11. APPENDIX 7 (Prior Agreements) is a complete and accurate list of all Isis In-License Agreements and all agreements between Isis and Third Parties as of the Effective Date with respect to the Exclusive Targets included in this Agreement as of the Effective Date, that create material Third Party Obligations that affect the rights granted by Isis to AstraZeneca under this Agreement. The Prior Agreements have not been materially amended or extended since first being placed in the Isis data room to which AstraZeneca was given access during the negotiation of this Agreement and subject to redactions represent a true and complete and accurate copy thereof, and any such redactions are of information not necessary to disclose to understand the implications of such Prior Agreements to this Agreement; and

8.2.12. Isis has not conducted any clinical studies with the Compounds and has conducted, and has required its contractors and consultants to conduct, any and all preclinical studies related to the Compounds in compliance with good laboratory and clinical practices and cGMP and Applicable Law, in each case as applicable under the laws and regulations of the country and the state and local government wherein such activities were conducted.

8.3. **Update to Warranties**. On a Collaboration Target-by-Collaboration Target basis, if at the time Isis delivers a Lead Candidate Data Package under Section 1.14.1 or at any time during the Evaluation Period with respect to such Target (each, a "***Bring-Down Date***"), Isis has Knowledge that any of the representations or warranties set forth in Section 8.2 are not true and accurate as at such Bring-Down Date with respect to such Target or any then existing Compounds for such Target (including any identified after the Effective Date), Isis will notify AstraZeneca of the relevant facts or circumstances as soon as practicable but no later than [***]` before the applicable Collaboration Program License Right Deadline.

8.4. **Additional Covenants of Isis**. Isis hereby covenants to AstraZeneca that, during the Agreement Term:

8.4.1. Isis will promptly amend APPENDIX 4 (Isis Core Technology Patents), APPENDIX 5 (Isis Manufacturing and Analytical Patents), APPENDIX 6 (Isis Product-Specific Patents and submit such amended Appendix to AstraZeneca 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 Appendices.

8.4.2. Isis will promptly notify AstraZeneca if it becomes aware of any agreement that should have been identified as a Prior Agreement or an Isis In-License Agreement and shall provide AstraZeneca with a copy of such agreement. With AstraZeneca's written consent, APPENDIX 3 (Isis In-License Agreements) or APPENDIX 7 (Prior Agreements) will be amended to include any such omitted agreement.

8.4.3. Isis will maintain and not breach any Isis In-License Agreement or any other agreement with Third Parties entered into after the Execution Date that provide a grant of rights from such Third Party to Isis that are Controlled by Isis and are licensed or that Isis believes may become subject to a license from Isis to AstraZeneca for any Exclusive Target, Lead Candidate or Product and will not amend, modify or terminate any such agreement in a manner that would adversely affect AstraZeneca's rights hereunder without first obtaining AstraZeneca's written consent, which consent may be withheld in AstraZeneca's sole discretion.

8.5. **DISCLAIMER OF WARRANTY. EXCEPT FOR THE EXPRESS WARRANTIES SET FORTH IN THIS ARTICLE 8, ASTRAZENECA AND ISIS MAKE NO REPRESENTATIONS AND GRANT NO WARRANTIES, EXPRESS OR IMPLIED, EITHER IN FACT OR BY OPERATION OF LAW, BY STATUTE OR OTHERWISE, AND ASTRAZENECA AND ISIS EACH SPECIFICALLY DISCLAIM ANY WARRANTIES, WHETHER WRITTEN OR ORAL, OR EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF QUALITY, MERCHANTABILITY OR FITNESS FOR A PARTICULAR USE OR PURPOSE OR ANY WARRANTY AS TO THE VALIDITY OF ANY PATENT RIGHTS OR THE NON-INFRINGEMENT OF ANY INTELLECTUAL PROPERTY RIGHTS OF THIRD PARTIES.**

ARTICLE 9.
INDEMNIFICATION; INSURANCE

9.1. **Indemnification by AstraZeneca**. AstraZeneca agrees to defend Isis, its Affiliates and their respective directors, officers, stockholders, employees and agents, and their respective successors, heirs and assigns (collectively, the "***Isis Indemnitees***"), and will indemnify and hold harmless the Isis Indemnitees, from and against any liabilities, losses, costs, damages, fees or expenses payable to a Third Party, and reasonable attorneys' fees and other legal expenses with respect thereto (collectively, "***Losses***") arising out of any claim, action, lawsuit or other proceeding by a Third Party (collectively, "***Third Party Claims***") brought against any Isis Indemnitee and resulting from or occurring as a result of: (a) any activities conducted by an AstraZeneca employee, consultant or (sub)contractor in the performance of the AstraZeneca Conducted Activities, (b) the Development, Manufacture or Commercialization of any Product by AstraZeneca or its Affiliates, Sublicensees, Distributors, Compulsory Sublicensees (but only to the extent AstraZeneca is indemnified by such Compulsory Sublicensee) or contractors, (c) any breach by AstraZeneca of any of its representations, warranties or covenants pursuant to this Agreement, or (d) the negligence or willful misconduct of AstraZeneca or any AstraZeneca Affiliate or Sublicensee in the performance of this Agreement; *except* in any such case to the extent such Losses result from: (i) the negligence or willful misconduct of any Isis Indemnitee, (ii) any breach by Isis of any of its representations, warranties, covenants or obligations pursuant to this Agreement or the MSA, or (iii) any breach of Applicable Law by any Isis Indemnitee.

9.2. **Indemnification by Isis**. Isis agrees to defend AstraZeneca, its Affiliates and their respective directors, officers, stockholders, employees and agents, and their respective successors, heirs and assigns (collectively, the "***AstraZeneca Indemnitees***"), and will indemnify and hold harmless the AstraZeneca Indemnitees, from and against any Losses arising out of Third Party Claims brought against any AstraZeneca Indemnitee and resulting from or occurring as a result of: (a) any activities conducted by an Isis employee, consultant or (sub)contractor in the performance of the Isis Conducted Activities; (b) any breach by Isis of any of its representations, warranties or covenants pursuant to this Agreement, (c) the negligence or willful misconduct of any Isis Indemnitee or any (sub)contractor of Isis in the performance of this Agreement, or (d) the Development, Manufacture or Commercialization of any Discontinued Product by Isis or its Affiliates, Sublicensees, Distributors or contractors; *except* in any such case to the extent such Losses result from: (i) the negligence or willful misconduct of any AstraZeneca Indemnitee, (ii) any breach by AstraZeneca of any of its representations, warranties, covenants or obligations pursuant to this Agreement or the MSA, or (iii) any breach of Applicable Law by any AstraZeneca Indemnitee.

9.3. **Notice of Claim**. All indemnification claims provided for in Section 6.12.3, Section 9.1, Section 9.2 and Section 10.3.2(a) will be made solely by such Party to this Agreement (the "***Indemnified Party***"). The Indemnified Party will give the indemnifying Party prompt written notice (an "***Indemnification Claim Notice***") of any Losses or the discovery of any fact upon which the Indemnified Party intends to base a request for indemnification under Section 9.1 or Section 9.2, but in no event will the indemnifying Party be liable for any Losses to the extent such Losses result from any delay in providing such notice. Each Indemnification Claim Notice must contain a description of the claim and the nature and amount of such Loss (to the extent that the nature and amount of such Loss is known at such time). The Indemnified Party will furnish promptly to the indemnifying Party copies of all papers and official documents received in respect of any Losses and Third Party Claims.

9.4. **Defense, Settlement, Cooperation and Expenses**.

9.4.1. **Control of Defense**. At its option, the indemnifying Party may assume the defense of any Third Party Claim by giving written notice to the Indemnified Party within 30 days after the indemnifying Party's receipt of an Indemnification Claim Notice. The assumption of the defense of a Third Party Claim by the indemnifying Party will not be construed as an acknowledgment that the indemnifying Party is liable to indemnify the Indemnified Party in respect of the Third Party Claim, nor will it constitute a waiver by the indemnifying Party of any defenses it may assert against the Indemnified Party's claim for indemnification. Upon assuming the defense of a Third Party Claim, the indemnifying Party may appoint as lead counsel in the defense of the Third Party Claim any legal counsel selected by the indemnifying Party. In the event the indemnifying Party assumes the defense of a Third Party Claim, the Indemnified Party will as soon as is reasonably possible deliver to the indemnifying Party all original notices and documents (including court papers) received by the Indemnified Party in connection with the Third Party Claim. Should the indemnifying Party assume the defense of a Third Party Claim, except as provided in this Section 9.4.1, the Indemnified Party will be responsible for the legal costs or expenses subsequently incurred by such Indemnified Party in connection with the analysis, defense or settlement of the Third Party Claim.

9.4.2. **Right to Participate in Defense**. Without limiting Section 9.4.1, any Indemnified Party will be entitled to participate in, but not control, the defense of such Third Party Claim and to employ counsel of its choice for such purpose; *provided, however*, that such employment will be at the Indemnified Party's own cost and expense unless (a) the employment thereof has been specifically authorized by the indemnifying Party in writing, (b) the indemnifying Party has failed to assume the defense and employ counsel in accordance with Section 9.4.1 (in which case the Indemnified Party will control the defense), or (c) the interests of the Indemnified Party and the indemnifying Party with respect to such Third Party Claim are sufficiently adverse to prohibit the representation by the same counsel of both Parties under Applicable Law, ethical rules or equitable principles in which case the indemnifying Party will be responsible for any such costs and expenses of counsel for the Indemnified Party.

9.4.3. **Settlement**. With respect to any Third Party Claims relating solely to the payment of money damages in connection with a Third Party Claim and that will not admit liability or violation of Law on the part of the Indemnified Party or result in the Indemnified Party's becoming subject to injunctive or other relief or otherwise adversely affecting the business of the Indemnified Party in any manner (such as granting a license or admitting the invalidity of a Patent Right Controlled by an Indemnified Party), and as to which the indemnifying Party will have acknowledged in writing the obligation to indemnify the Indemnified Party hereunder, the indemnifying Party will have the sole right to consent to the entry of any judgment, enter into any settlement or otherwise dispose of such Loss, on such terms as the indemnifying Party, in its sole discretion, will deem appropriate. With respect to all other Losses in connection with Third Party Claims, where the indemnifying Party has assumed the defense of the Third Party Claim in accordance with Section 9.4.1, the indemnifying Party will have authority to consent to the entry of any judgment, enter into any settlement or otherwise dispose of such Loss provided it obtains the prior written consent of the Indemnified Party (which consent will not be unreasonably withheld). The indemnifying Party will not be liable for any settlement, consent to entry of judgment, or other disposition of a Loss by an Indemnified Party that is reached without the written consent of the indemnifying Party. Regardless of whether the indemnifying Party chooses to defend or prosecute any Third Party Claim, no Indemnified Party will admit any liability with respect to or settle, compromise or discharge, any Third Party Claim without the prior written consent of the indemnifying Party, such consent not to be unreasonably withheld.

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

9.4.5. **Costs and Expenses**. Except as provided above in this Section 9.4, the costs and expenses, including attorneys' fees and expenses, incurred by the Indemnified Party in connection with any claim will be reimbursed on a Calendar Quarter basis by the indemnifying Party, without prejudice to the indemnifying Party's right to contest the Indemnified Party's right to indemnification and subject to refund in the event the indemnifying Party is ultimately held not to be obligated to indemnify the Indemnified Party.

9.5. **Insurance**.

9.5.1. **Isis' Insurance Obligations**. Isis will maintain, at its cost, reasonable insurance against liability and other risks associated with its activities contemplated by this Agreement, including but not limited to its indemnification obligations herein, in such amounts and on such terms as are customary for prudent practices for biotech companies of similar size and with similar resources in the pharmaceutical industry for the activities to be conducted by it under this Agreement taking into account the scope of development of products. Isis will furnish to AstraZeneca evidence of any insurance required under this Section 9.5.1, upon request.

9.5.2. **AstraZeneca's Insurance Obligations**. AstraZeneca hereby represents and warrants to Isis that it will maintain, at its cost, reasonable insurance against liability and other risks associated with its activities contemplated by this Agreement (including product liability), including but not limited to its indemnification obligations herein, in such amounts and on such terms as are customary for prudent practices for large companies in the pharmaceutical industry for the activities to be conducted by AstraZeneca under this Agreement. AstraZeneca will maintain such insurance or self-insurance throughout the Agreement Term and for five years thereafter, and will furnish to Isis evidence of such insurance, upon request.

9.6. LIMITATION OF CONSEQUENTIAL DAMAGES. EXCEPT FOR (a) CLAIMS OF A THIRD PARTY THAT ARE SUBJECT TO INDEMNIFICATION UNDER THIS ARTICLE 9 OR SECTION 10.3.2(a), (b) CLAIMS ARISING OUT OF A PARTY'S WILLFUL MISCONDUCT, (c) A PARTY'S BREACH OF ARTICLE 3, OR A BREACH OF SECTION 10.3.1(a) BY ASTRAZENECA 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.

9.7. Anti-Bribery and Corruption Compliance.

9.7.1. Each Party agrees, on behalf of itself, its officers, directors and employees and on behalf of its Affiliates that it will, and will use its diligent efforts to procure that its agents, representatives, consultants and subcontractors hired for activities undertaken for or in connection with the performance of this Agreement, (together with such Party, the "***Party Representatives***") for the performance of its obligations hereunder:

Party Representatives will not directly or indirectly pay, offer or promise to pay, or authorize the payment of any money, or give, offer or promise to give, or authorize the giving of anything else of value, to:

(1) any Government Official in order to influence official action;

(2) any Person (whether or not a Government Official) (i) to influence such Person to act in breach of a duty of good faith, impartiality or trust ("acting improperly"), (ii) to reward such Person for acting improperly, or (iii) where such Person would be acting improperly by receiving the money or other thing of value;

(3) any other Person while knowing or having reason to know that all or any portion of the money or other thing of value will be paid, offered, promised or given to, or will otherwise benefit, a Government Official in order to influence official action for or against either Party in connection with the matters that are the subject of this Agreement; or

(4) any Person to reward that Person for acting improperly or to induce that Person to act improperly.

9.7.2. Each Party will not and will use diligent efforts to procure that its Party Representatives will not, directly or indirectly, solicit, receive or agree to accept any payment of money or anything else of value in violation of the Anti-Corruption Laws.

9.7.3. Each Party acknowledges that its undertakings given in Sections 9.7.1 and 9.7.2 are material to the other Party in entering into a relationship with such Party.

9.7.4. Each Party, on behalf of itself and its Party Representatives, represents and warrants to the other Party that for the term of this Agreement and six years thereafter, it will and will use diligent efforts to procure that its Party Representatives keep and maintain accurate books and reasonably detailed records in connection with the performance of its obligation under this Agreement including all records required to establish compliance with Sections 9.7.1 and 9.7.2 above.

9.7.5. Each Party will promptly provide the other Party with written notice of the following events: (A) upon becoming aware of any material breach or violation by it or its Party Representatives of any representation, warranty or undertaking set forth in Sections 9.7.1 and 9.7.2; and (B) upon receiving a formal notification that it is the target of a formal investigation by a Relevant Authority for a Material Anti-Corruption Law Violation or upon receipt of information from any of its Party Representatives connected with this Agreement that any of them is the target of a formal investigation by a Relevant Authority for a Material Anti-Corruption Law Violation.

9.7.6. For the term of this Agreement and six years thereafter, each Party will for the purpose of auditing and monitoring the performance of its compliance with the Agreement and particularly this Section 9.7 permit the other Party, its Affiliates, any auditors of any of them and any Regulatory Authority to have access to any premises of such Party and to the extent that such Party is able to secure such access, its Party Representatives in each case used in connection with this Agreement, together with a right to access personnel and records that relate to this Agreement ("***Audit***").

9.7.7. Each Party will be responsible for any breach of any representation, warranty or undertaking in this Section 9.7 or of the Anti-Corruption Laws by any of its Party Representatives.

9.7.8. Each Party may disclose the terms of this Agreement or any action taken under this Section 9.7 to prevent a potential violation or continuing violation of applicable Anti-Corruption Laws, including the identity of the other Party and the payment terms, to any governmental authority if such Party determines, upon advice of counsel, that such disclosure is necessary.

ARTICLE 10.
TERM; TERMINATION

10.1. **Agreement Term; Expiration**. This Section 10.1, ARTICLE 11 and ARTICLE 12 of this Agreement will become effective on the Execution Date and the remainder of this Agreement will become 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. where there are no Collaboration Targets designated under Section 1.10 by the later of (i) the expiration of the Disease Research Term or (ii) the last date on which any former High Interest Target could become a Collaboration Target pursuant to Section 1.10.3(c);

10.1.2. where there are no Development Candidates designated under Section 1.14 by the later of (i) the expiration of the Collaboration Program Term, and (ii) the last date on which the exercise of a Carryover Option could occur;

10.1.3. where all Collaboration Program License Rights (including those that could arise pursuant to Section 1.10.3(c) and Section 1.14.3(e)) have expired unexercised;

10.1.4. on a country-by-country and Product-by-Product basis, on the date of expiration of all payment obligations by AstraZeneca under this Agreement with respect to such Product in such country; or

10.1.5. in its entirety upon the expiration of all payment obligations by AstraZeneca under this Agreement with respect to the last Product in all countries pursuant to Section 10.1.4.

The period from the Effective Date until the date of expiration of this Agreement pursuant to this Section 10.1 or earlier termination of this Agreement pursuant to Section 10.2, is the "***Agreement Term***." If any antitrust clearance required in accordance with Section 12.5 is not obtained by December 31, 2015, this Agreement, including this Section 10.1, ARTICLE 11 and ARTICLE 12 will automatically expire.

10.2. **Termination of the Agreement**.

10.2.1. **AstraZeneca's Termination for Convenience or Change of Control**.

(a) **Termination for Convenience or with respect to** [***]. At any time following payment by AstraZeneca of the upfront fee under Section 6.1, subject to Section 10.3.1 below, AstraZeneca will be entitled to terminate this Agreement:

(i) in its entirety or in part on a Collaboration Target-by-Collaboration Target basis for convenience by providing 90 days written notice to Isis of such termination; or

(ii) with respect to the [***] Program as set forth in Section 6.6.2 on written notice to Isis of such termination.

(b) **Change of Control Event**.

(i) Prior to the Collaboration Program License Right Deadline for a Collaboration Target, AstraZeneca will have the right to terminate this Agreement in whole or in part with respect to one or more Collaboration Targets for which AstraZeneca has not exercised its Collaboration Program License Right, immediately upon written notice to Isis provided at any time within 30 Business Days following notification by Isis to AstraZeneca of the closing of a Change of Control Event (and Isis will be obliged to give notice on such closing, and in the event it fails to do so, AstraZeneca's right to terminate may be exercised within 90 Business Days of such closing coming to AstraZeneca's Knowledge), if such closing occurs during the Collaboration Program Term.

(ii) If at AstraZeneca's discretion, AstraZeneca decides not to terminate this Agreement with respect to a particular Collaboration Target pursuant to this Section 10.2.1(b) following the closing of a Change of Control Event during the Collaboration Program Term, then, subject to the below provisions in this Section 10.2.1, Isis' and AstraZeneca's obligations under ARTICLE 1 to perform the relevant program on such Collaboration Target will remain and Isis (or its successor) will use Commercially Reasonable Efforts to perform the relevant program on such Collaboration Target in accordance with this Agreement while, to the extent reasonably practicable, maintaining confidentiality of AstraZeneca's Confidential Information from any entity acquiring Isis as a result of the Change of Control Event. As soon as reasonably possible after the public announcement of such a Change of Control Event, Isis (or its successor) and AstraZeneca will meet to discuss in good faith how Isis (or its successor) will continue to perform its obligations under this Agreement with respect to any Collaboration Targets for which AstraZeneca has not exercised its Collaboration Program License Right so that AstraZeneca can consider whether to exercise its rights of termination under this Section 10.2.1(b).

(iii) If AstraZeneca does not exercise its right of termination, AstraZeneca will have the right, by providing Isis with written notice within 30 Business Days following notification by Isis to AstraZeneca of the closing of a Change of Control Event, to require that Isis ceases performing any or certain activities and co-operate and take such measures as may be requested to ensure a prompt and smooth transition of such activities to AstraZeneca or its designee. AstraZeneca will be entitled to deduct an amount equal to the [***] from its next applicable milestone or license fee payment as applicable. Without prejudice to the foregoing, if requested by AstraZeneca such measures will include a technology transfer pursuant to the provisions of Section 4.8 and/or Section 4.1.2(c), in either case without charge to AstraZeneca.

(iv) Furthermore, if the surviving entity following such Change of Control Event is clinically developing or commercializing a product that is directly competing with a Product under this Agreement, then subject to Section 3.3, (i) the development or commercialization of such directly competing product by such surviving entity will not be a violation of Isis' exclusivity covenants under Section 3.1 if such product was being developed or commercialized by the Acquiring Party prior to the Change of Control Event, and (ii) solely with respect to the Product that is subjected to such competition, Section 5.2 shall apply.

10.2.2. Termination for Material Breach.

(a) **AstraZeneca's Right to Terminate**. If AstraZeneca has reason to believe 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 10.2.3 below), then AstraZeneca may deliver notice of such material breach to Isis. If the breach is curable, Isis will have 60 days to cure such breach. If Isis fails to cure such breach within the 60 day period, or if the breach is not subject to cure, AstraZeneca may terminate this Agreement in its entirety if such breach relates to this Agreement in its entirety, or in relevant part on a Product-by-Product, Collaboration Target-by-Collaboration Target basis if such breach does not relate to this Agreement in its entirety, by providing written notice to Isis.

(b) **Isis' Right to Terminate**. If Isis has reason to believe that AstraZeneca is in material breach of this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under ARTICLE 1 or Section 5.1, which is governed by Section 10.2.3 below), then Isis may deliver notice of such material breach to AstraZeneca. If the breach is curable, AstraZeneca will have 60 days to cure such breach (except to the extent such breach involves the failure to make a payment when due, which breach must be cured within 30 days following such notice). If AstraZeneca fails to cure such breach within the 60 day or 30 day period, as applicable, or if the breach is not subject to cure, Isis may terminate this Agreement in its entirety if such breach relates to this Agreement in its entirety, or in relevant part on a Product-by-Product, Collaboration Target-by-Collaboration Target basis if such breach does not relate to this Agreement in its entirety, by providing written notice to AstraZeneca.

10.2.3. **Remedies for Failure to Use Commercially Reasonable Efforts**.

(a) If Isis fails to use Commercially Reasonable Efforts as contemplated in ARTICLE 1 (as determined in accordance with Section 12.1), AstraZeneca will notify Isis and, within 30 days thereafter, Isis and AstraZeneca 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 in ARTICLE 1 and such failure constitutes a material breach of this Agreement, then subject to Section 10.2.4 below, AstraZeneca will have the right, at its sole discretion, to terminate this Agreement in whole or in part on a Collaboration Target-by-Collaboration Target basis.

(b) If AstraZeneca fails to use Commercially Reasonable Efforts as contemplated in ARTICLE 1 or Section 5.1 (as determined in accordance with Section 12.1), Isis will notify AstraZeneca and, within 30 days thereafter, Isis and AstraZeneca 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 AstraZeneca's use of Commercially Reasonable Efforts in ARTICLE 1 or Section 5.1. Following such a meeting, if AstraZeneca fails to use Commercially Reasonable Efforts as contemplated in ARTICLE 1 or Section 5.1, and such failure constitutes a material breach of this Agreement then subject to Section 10.2.4 below, Isis will have the right, at its sole discretion, to terminate this Agreement in part on a Collaboration Target-by-Collaboration Target basis.

10.2.4. **Disputes Regarding Material Breach**. Notwithstanding the foregoing, if the Breaching Party in Section 10.2.2 or Section 10.2.3 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 respectively such 60 day cure period or 30 day notice period, the Non-Breaching Party will not have the right to terminate this Agreement in accordance with Section 10.2.2 or Section 10.2.3, unless and until it has been determined in accordance with Section 12.1 that this Agreement was materially breached by the Breaching Party and the Breaching Party fails to cure such breach within 30 days following such determination. It is understood and acknowledged that during the pendency of such dispute, all the terms and conditions of this Agreement will remain in effect and the Parties will continue to perform all of their respective obligations hereunder, including satisfying any payment obligations.

10.2.5. **Termination of a Licensed Program**. Once AstraZeneca has exercised its Collaboration Program License Rights with respect to a Collaboration Target, neither Party shall be entitled to terminate that Licensed Program pursuant to Sections 10.2.2 or 10.2.3 unless the material breach or failure to use Commercially Reasonable Efforts is with respect to such Licensed Program and any such breach or failure shall be determined on a Licensed Program-by-Licensed Program basis.

10.2.6. **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 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***") or analogous provisions of Applicable Law outside the US licenses of rights to "intellectual property" as defined in Section 101(56) of the Bankruptcy Code or analogous provisions of Applicable Law outside the US. The Parties will retain and may fully exercise all of their respective rights and elections under the Bankruptcy Code or analogous provisions of Applicable Law outside the US. Upon the commencement of a bankruptcy proceeding 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 all embodiments which, if not already in its possession, will be promptly delivered to the non-bankrupt Party upon written request.

10.2.7. **Termination for Patent Challenge**. Isis may terminate this Agreement if AstraZeneca disputes, or assists any Third Party to dispute, the validity of any Licensed Patent, in a patent re-examination, inter-partes review, post grant or other patent-office proceeding, opposition, litigation, or other court proceeding and, within 30 days written notice from Isis, AstraZeneca fails to rescind any and all of such actions, *provided however* that, nothing in this clause prevents AstraZeneca from taking any of the actions referred to in this clause and *provided further* that Isis will not have the right to terminate if AstraZeneca:

(a) asserts invalidity as a defense in any court proceeding brought by Isis asserting infringement of a Licensed Patent; or

(b) Acquires a Third Party that has an existing challenge, whether in a court or administrative proceeding, against a Licensed Patent; or

(c) licenses a product for which Isis has an existing challenge, whether in a court or administrative proceeding, against a Licensed Patent.

10.3. **Consequences of Expiration or Termination of this Agreement**.

10.3.1. **Consequence of Termination of this Agreement**. If this Agreement is terminated by a Party in accordance with Section 10.2, in its entirety or on a Collaboration Target-by-Collaboration Target basis at any time and for any reason, the following terms will apply to any such termination, but only to the extent of any such termination (i.e., with respect to the terminated Collaboration Program or Licensed Program (the "***Terminated Program***" and its Target, the "***Terminated Target***" and the Products under such Terminated Program at the termination Date, the "***Discontinued Products***"), or in its entirety):

(a) **Licenses**. The licenses granted by Isis to AstraZeneca under this Agreement will terminate and, AstraZeneca and its Affiliates and, subject to Section 4.1.2(d), its Sublicensees will cease selling Discontinued Products under such licenses; *provided, that* (i) AstraZeneca and its Affiliates and Sublicensees will have the right to sell any remaining inventory of Discontinued Product over a period of no greater than six months after the effective date of such termination, and AstraZeneca will pay Isis royalties in accordance with Section 6.7 on the Net Sales of such inventory of such Products, to the extent not already paid; and (ii) if there are any Clinical Studies being conducted at the date of termination, AstraZeneca shall be entitled to continue Developing and Manufacturing Compounds and Products to the extent and for the period necessary to effect an orderly transfer or wind down of such Clinical Studies in a timely manner and in accordance with all Applicable Laws.

(b) **Collaboration Program License Rights**. If not exercised prior to the date of termination, AstraZeneca's Collaboration Program License Right will terminate with respect to any Terminated Target.

(c) **Exclusivity**. Neither Party will have any further obligations under Section 3.1 of this Agreement insofar as it relates to a Terminated Target.

(d) **Collaboration Plans**. Except as expressly stated to survive under Section 10.3.1(h), neither Party will have any further obligations with respect to the Terminated Program under the Collaboration Plan(s).

(e) **Responsibility for Discontinued Products**. If a Product becomes a Discontinued Product, except as expressly provided in this Section 10.3, AstraZeneca will have no further obligations or responsibilities with respect to such Product and except for any activities undertaken by AstraZeneca, its Affiliates, Sublicensees or Distributors pursuant to Section 10.3.1(a) or prior to the date of termination, Isis will be responsible for all liabilities relating to the Development, Manufacture and Commercialization of a Discontinued Product by or on behalf of Isis, its Affiliates, Sublicensees or distributors following the date of such termination.

(f) **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 to which it does not retain rights under the surviving provisions of this Agreement. 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. Each Party will also be permitted to retain such additional copies of or any computer records or files containing the other Party's Confidential Information that have been created solely by automatic archiving and back-up procedures, to the extent created and retained in a manner consistent with the retaining Party's standard archiving and back-up procedures, but not for any other use or purpose. All Confidential Information shall continue to be subject to the terms of this Agreement for the period set forth in Section 11.1.

(g) **Accrued Rights**. Termination of this Agreement for any reason will be without prejudice to any rights or financial compensation that will have accrued to the benefit of a Party prior to such termination. Such termination will not relieve a Party from obligations that are expressly indicated to survive the termination 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.

(h) **Survival**. The following provisions of this Agreement will survive the expiration or earlier termination of this Agreement: Section 1.10 (Process for Designating High Interest Targets as Collaboration Targets) (but only with respect to the Parties' rights and obligations related to restoring a Target to this Agreement as a Collaboration Target and the exclusivity covenants in effect as of the date of such expiration or earlier termination of this Agreement), Section 1.11 (End of Core Research Term) (but only with respect to the licenses and other rights granted therein), Section 1.12 (End of the Disease Research Term) (but only with respect to the provisions of Section 1.10 referenced therein), Section 1.14 (Process for Designating Development Candidates) (but only with respect to the Parties' rights and obligations related to restoring a Target and Compounds to this Agreement, the licenses and other rights granted therein and the exclusivity covenants in effect as of the date of such expiration or earlier termination of this Agreement), Section 1.15 (Expiration of Collaboration Program Term) (but only with respect to the provisions of Section 1.14 referenced therein), Section 1.16 (Exclusive Right to Obtain or Maintain Exclusive Licenses to Development Candidates) (but only with respect to Development Candidates restored to this Agreement), Section 1.16.4 (No Exercise) (but only with respect to the licenses and other rights granted therein and AstraZeneca's exclusivity covenants in effect as of the date of such expiration or earlier termination of this Agreement), Section 4.1.2(d) (Effect of Termination on Sublicenses), Section 4.1.3 (Consequence of Natural Expiration of this Agreement), Section 4.1.4 (No Implied Licenses), Section 4.2.2 (Grant-Back to Isis of Isis Product-Specific Patents), Section 4.3 (Non-Exclusive Technology License Grant to AstraZeneca), Section 4.4 (Cross Licenses Under Collaboration Intellectual Property), Section 4.5 (Interaction of Licenses), Section 6.7.2(d) (End of Royalty Obligation), Section 6.10.3 (Records Retention), Section 6.11 (Audits), Section 6.12 (Taxes), Section 6.13 (Interest), Section 7.1.1 (Isis Technology and AstraZeneca Technology), Section 7.1.2 (Collaboration Technology), Section 7.1.4 (Jointly Owned Collaboration Technology), Section 7.2.3 (Jointly-Owned Collaboration Patents) (but subject to Section 10.3.2(e), if applicable), Section 7.3.1 (Jointly-Owned Collaboration Patents) (but subject to Section 10.3.2(e), if applicable) ARTICLE 9 (Indemnification; Insurance) (but excluding Section 9.7), Section 10.3 (Consequences of Expiration or Termination of this Agreement), ARTICLE 11 (Confidentiality), ARTICLE 12 (Miscellaneous) and APPENDIX 1 (Definitions) (to the extent definitions are embodied in the foregoing listed Articles and Sections).

10.3.2. **Isis: Special Consequences of Certain Terminations**. If (A) AstraZeneca terminates the Agreement under Section 10.2.1 or (B) Isis terminates this Agreement under Section 10.2.2(b), Section 10.2.3(b), Section 10.2.6, or Section 10.2.7, then, in addition to the terms set forth in Section 10.3.1, the following additional terms will also apply but only with respect to the Terminated Program, Terminated Target and Discontinued Product:

(a) Subject to Section 10.3.2(g) and Section 10.3.2(h), AstraZeneca will and hereby does grant to Isis:

(1) a sublicensable, worldwide, exclusive license or sublicense, as the case may be, under all AstraZeneca Technology (excluding AstraZeneca Background Intellectual Property) Controlled by AstraZeneca as of the date of such reversion that Covers the Discontinued Product as Developed or Commercialized by AstraZeneca or its Affiliates as at such date; and

(2) a sublicensable, worldwide, non-exclusive license or sublicense, as the case may be, under all AstraZeneca Background Intellectual Property Controlled by AstraZeneca as of the date of such reversion that Covers the Discontinued Product as Developed or Commercialized by AstraZeneca or its Affiliates as at such date;

in each case solely to Develop, make, have made, use, sell, offer for sale, have sold, import and otherwise Commercialize the Discontinued Product in the Field (such licenses will be sublicensable by Isis in accordance with Section 4.1.2, *mutatis mutandis*); and *provided that* Isis will, (y) in accordance with ARTICLE 9, indemnify and hold harmless AstraZeneca and its Affiliates and Sublicensees from any Losses arising out of Third Party Claims with respect to the Exploitation of such Discontinued Product; and (z) be responsible for (and to the extent paid by AstraZeneca, indemnify and hold harmless AstraZeneca and its Affiliates for) all licensing costs and payments payable to Third Parties for technology used in a Discontinued Product of which AstraZeneca has made Isis aware unless Isis notifies AstraZeneca that it does not wish a license under such technology and Isis ceases to use such technology on or prior to such notification, in each case (x) and (y) with respect to the Exploitation of such Discontinued Product under such licenses that accrue after the date of such termination.

(b) AstraZeneca will assign back to Isis any Patent Rights that relate to the Discontinued Product previously assigned by Isis to AstraZeneca under this Agreement;

(c) AstraZeneca will transfer to Isis for use with respect to the Development and Commercialization of the Discontinued Product, any Know-How, data, results, regulatory information, pricing and market access strategy information, health economic study information, material communications with payors, filings, and files in the possession of AstraZeneca, or copies thereof, as of the date of such termination or reversion that relate solely to such Discontinued Product;

(d) AstraZeneca will grant to Isis a non-exclusive, royalty-free, fully paid up license under any trademarks that are specific to a Discontinued Product solely for use with such Discontinued Product; *provided, however*, that in no event will AstraZeneca have any obligation to license to Isis any trademarks used by AstraZeneca both in connection with the Product and in connection with the sale of any other product or service, including any AstraZeneca- or AstraZeneca-formative marks;

(e) Isis will control and be responsible for all aspects of the Prosecution and Maintenance of all Jointly-Owned Collaboration Patents and AstraZeneca will provide Isis with (and will instruct its counsel to provide Isis with) all of the information and records in AstraZeneca's and its counsel's possession related to the Prosecution and Maintenance of such Jointly-Owned Collaboration Patents, in each case only in respect of the Discontinued Product;

(f) upon Isis' written request pursuant to a mutually agreed supply agreement, AstraZeneca will sell to Isis any bulk API and finished Product in AstraZeneca's possession related to the Compounds that are the subject of the termination at the time of such termination, at a price equal to AstraZeneca's cost at the time such material was produced;

(g) If Isis or any of its Affiliates or Sublicensees Commercializes a Discontinued Product for which AstraZeneca has paid Isis the license fee under Section 6.2 (or, with respect to [***], the [***] CD Milestone) for a Product, then in each such case, following the First Commercial Sale of such Discontinued Product by Isis or its Affiliates or Sublicensees, Isis will pay AstraZeneca a royalty of [***]% of Annual worldwide Net Sales of such Discontinued Product until [***];

(h) If there are any licensed rights granted by AstraZeneca to Isis under Section 10.3.2(a)(2), the Parties will negotiate in good faith regarding a reasonable royalty for such Discontinued Product (not to exceed [***]%) of Annual worldwide Net Sales of such Discontinued Product) to be paid by Isis to AstraZeneca for Discontinued Products covered by such licensed rights, with such royalty payments beginning on the date [***] and ending on the earlier of (y) [***], or (z) [***];

(i) for the purposes of clauses (g) and (h), Net Sales shall mean Net Sales by Isis, its Affiliates and Sublicensees, *provided, that* any definition of "net sales" agreed to by Isis and a Sublicensee in an arms-length sublicense agreement for the Commercialization of a Discontinued Product will be used to calculate net sales of such Discontinued Product sold by Isis' Sublicensees on which royalties are payable by Isis to AstraZeneca hereunder; and

(j) for clarity, the licenses granted by AstraZeneca pursuant to this Section 10.3.2 do not include any intellectual property rights relating to compounds that are not Compounds.

10.3.3. AstraZeneca: Special Consequences of Certain Terminations.

(a) If AstraZeneca terminates this Agreement under Section 10.2.2(a), Section 10.2.3(a) or Section 10.2.6, all of the provisions of Section 10.3.1 will apply, *except that* AstraZeneca, its Affiliates, Sublicensees and Distributors will have the right to sell any remaining inventory of Product, and AstraZeneca will pay Isis royalties in accordance with Section 6.7 on the Net Sales of such inventory of such Products to the extent not already paid.

(b) If AstraZeneca has the right to terminate this Agreement under Section 10.2.2(a), Section 10.2.3(a) or Section 10.2.6, but elects to continue the Agreement, the following provisions which will be effective upon AstraZeneca's notice of such election, will apply:

(i) AstraZeneca may require that Isis ceases performing any activities and co-operate and take such measures as may be requested to ensure a prompt and smooth transition of such activities to AstraZeneca or its designee; and may require that Isis cease to participate in the JSC. Without prejudice to the foregoing, if requested by AstraZeneca such measures will include a technology transfer pursuant to the provisions of Section 4.8 or Section 4.1.2(c), in either case without charge to AstraZeneca; and

(ii) any money damages that may be awarded to AstraZeneca arising from the circumstances which gave rise to the right to terminate, and any costs (the amount of such costs as mutually agreed in good faith by the Parties) incurred by AstraZeneca in connection with the transition of Isis' responsibilities under this Agreement to AstraZeneca or its designee may be set off against any monies owed by AstraZeneca to Isis as provided in Section 12.2.2.

10.3.4. The provisions of this Section 10.3 will not preclude any Party from pursuing all rights and remedies it may have hereunder or at law or in equity with respect to any breach of this Agreement, nor prejudice any Party's right to obtain performance of any obligation; *provided that* in assessing the remedies available to Isis, the rights transferred to Isis following a termination of this Agreement (in its entirety or with respect to a Termination Program and Discontinued Product) shall be taken into account. The Parties acknowledge and agree that the only rights that permit a Party to terminate this Agreement are set out in this ARTICLE 10.

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 Information disclosed by the other Party or its Affiliates (the "***Disclosing Party***").

11.2. **Prior Confidentiality Agreement**. The Mutual Confidential Disclosure Agreement executed by Isis and AstraZeneca on April 11, 2011 (including any and all amendments thereto) (the "***CDA***") will govern disclosures of Confidential Information (as defined in the CDA) between the Parties prior to the Execution Date in connection with the subject matter of this Agreement. All Confidential Information exchanged between the Parties on or after the Execution Date under this Agreement 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, Sublicensees, 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; (v) subject to the terms of any protective order the Disclosing Party is using to protect its own Confidential Information, to prosecute or defend litigation as permitted by this Agreement, or (vi) as mutually agreed to in writing by the Parties.

11.4. **Licensed Know-How**. Isis acknowledges AstraZeneca's interest in maintaining the confidentiality of Confidential Information that is Isis Know-How and specific to an Exclusive Target, Product and will take reasonable steps to protect such Confidential Information from unauthorized use or disclosure.

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

11.5.1. **Public Announcements – Generally**. On or promptly after each of the Execution Date and the Effective Date, the Parties will issue a joint press release announcing the existence of this Agreement in a form and substance agreed to in writing 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 11.5, each Party agrees not to issue any other press release or other public statement disclosing other information relating to this Agreement or the terms of this Agreement or the transactions contemplated hereby without the prior written consent of the other Party, which consent will not be unreasonably withheld or delayed.

11.5.2. **Use of Name**. Except as set forth in Section 11.5.8, 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.

11.5.3. **Notice of Significant Events**. Each Party will promptly notify (and where it has advance warning provide advance notice to) the other of any significant event related to a Product in a Major Market (including any data or regulatory advice or approval or reimbursement decision) so that the Parties may analyze the need to or desirability of publicly disclosing or reporting such event. Notwithstanding Section 11.5.1 above, any press release or other similar public communication (i) by Isis related to a Product will be submitted to AstraZeneca for review and approval at least three Business Days in advance of such proposed public disclosure, which approval will not be unreasonably withheld or delayed; and (ii) by AstraZeneca related to a Product's efficacy or safety data and/or results, regulatory advice or an approval or reimbursement decision in a Major Market, will be submitted to Isis for review (but shall not be subject to approval by Isis) at least three Business Days in advance of such proposed public disclosure.

11.5.4. **Disclosure of Information Related to Products**. The Party that has primary control of a Product (i.e., as of the Effective Date, Isis, with respect to all Products for which AstraZeneca has not exercised its Collaboration Program License Right, and with respect to any Licensed Program, AstraZeneca) has the sole right, consistent with its practice with its other products, to issue press releases or other similar public communications to disclose the progress and results regarding such Product to the public in order to satisfy its disclosure obligations under Applicable Law or to remain consistent with its normal public disclosure practices (but for clarity, in connection with the Collaboration Programs, such disclosure would not involve disclosing a Collaboration Target or a Development Candidate until such Development Candidate is in a Phase 1 Study); *provided, that* any proposed press release or other similar public communication by such controlling Party disclosing regulatory discussions, the efficacy or safety data or results related to the Product, (i) such controlling Party will submit such proposed communication to the non-controlling Party for review at least two Business Days in advance of such proposed public disclosure, (ii) the non-controlling Party will have the right to review and recommend changes to such communication, and (iii) the controlling Party will in good faith consider any changes that are timely recommended by the non-controlling Party. In addition, if at any time during such two Business Day review period, the other Party informs such Party that its proposed public disclosure discloses inventions made by either Party in the course of the Research or Development under this Agreement that have not yet been protected through the filing of a patent application, or the public disclosure 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 (x) delay such proposed publication for a period of time reasonably necessary to permit the timely preparation and first filing of patent application(s) on the information involved, or (y) to the extent permitted by Applicable Law, remove the identified information prior to disclosure. While the Parties acknowledge that it may be interpreted that there is overlap between this Section 11.5.4 and Section 11.5.5, for clarity, the Parties intend for this Section 11.5.4 to address public disclosures that are not primarily of a scientific or scholarly nature (which are meant to be disclosed in accordance with Section 11.5.5 below) but rather this Section 11.5.4 is designed to address more urgent disclosures required under Applicable Law or to provide investors with material information regarding Products or this Agreement in a timely manner so that they may make informed investment decisions in Isis' or AstraZeneca's stock.

11.5.5. **Scientific or Clinical Presentations**. Regarding any proposed scientific publications or public presentations related to summaries of results from the Collaboration Plans or any Clinical Studies generated by Isis or AstraZeneca for a Product, the Parties acknowledge that scientific lead time is a key element of the value of a Product under this Agreement and further agree to use Commercially Reasonable Efforts to control public scientific disclosures of the results of the Research or Development activities under this Agreement to prevent any potential adverse effect of any premature public disclosure of such results, for example, without limitation, intellectual property protection, competitive intelligence, prejudicing the optimal presentation at major meetings. For clarity, in connection with the Collaboration Programs, such disclosure would not involve disclosing a Collaboration Target or a Development Candidate until such Development Candidate is in a Phase 1 Study, unless agreed otherwise by the Parties. The IP Managers will establish a procedure for publication review and each Party will first submit to the other Party's IP Manger an early draft of all such publications or presentations, whether they are to be presented orally or in written form, at least 30 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 Plans. If, during such 30 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 30 day period, the other Party informs such Party that its proposed publication discloses inventions made by either Party in the course of the Research or Development under this Agreement that have not yet been protected through the filing of a patent application, or the public disclosure of such proposed publication could be expected to have a material adverse effect on any Patent Rights or Know-How solely owned or Controlled by such other Party, then such Party will either (i) delay such proposed publication for up to 60 days from the date the other Party informed such Party of its objection to the proposed publication, to permit the timely preparation and first filing of patent application(s) on the information involved or (ii) remove the identified disclosures prior to publication.

11.5.6. **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.

11.5.7. **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.

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

ARTICLE 12.
MISCELLANEOUS

12.1. Dispute Resolution.

12.1.1. Resolution by Senior Representatives. The Parties will seek to settle amicably any and all disputes, controversies or claims arising out of or in connection with this Agreement. Any dispute between the Parties, including any a failure to reach consensus on a matter within the JSC's decision-making authority will be promptly presented to the Executive Vice President of AstraZeneca's Innovative Medicines and Early Development (IMED) Biotech Unit and the Chief Operating Officer of Isis (the "***Senior Representatives***"), or their respective designees, for resolution. Such Senior Representatives, or their respective designees, will meet in-person or by teleconference as soon as reasonably possible thereafter, and use their good faith efforts to mutually agree upon the resolution of the dispute, controversy or claim.

12.1.2. Request for Arbitration. If after negotiating in good faith pursuant to Section 12.1.1, the Parties fail after good faith discussions undertaken within reasonable promptness, to reach an amicable agreement within 90 days, then either Party may upon written notice to the other submit to binding arbitration pursuant to Section 12.1.4(a) below; provided that any dispute within the JSC's decision-making authority whether or not resolved by the Senior Representatives will not be subject to arbitration. No statements made by either Party during such discussions will be used by the other Party or admissible in arbitration or any other subsequent proceeding for resolving the dispute.

12.1.3. Expert Determination for [***] **Development Candidate**.

(a) If the JSC fails to designate a [***] Development Candidate but Isis believes that a Lead Compound from the [***] Program satisfies the [***] Success Criteria such that AstraZeneca is not entitled to the benefit of the [***] described in Section 6.6.1 and such dispute (the "[***] ***Dispute***") is not resolved by the Senior Representatives in accordance with Section 12.1.1, either Party may initiate an expedited dispute resolution by Expert (as defined below) to resolve the matter by serving written notice thereof on the other Party (a "***Referral Notice***").

(b) Within [***] following any Referral Notice, the Parties will engage the services of an independent scientist with no less than 10 years' experience in drug discovery (the "***Expert***"), *provided that* if the Parties are unable to agree on who will be appointed as expert within such period, either Party may request the International Chamber of Commerce ("***ICC***") to appoint the Expert.

(c) The Expert will be directed to review the Lead Candidate Data Package provided to the JSC and to determine, within [***] of being provided such package, whether any Lead Compound from the [***] Program satisfies the [***] Success Criteria.

(d) The Expert will act as an expert and not as an arbitrator and the decision of the Expert shall be final and binding on both Parties. Any legal dispute regarding the scope, legal effect or validity of the determination shall be subject to the arbitration procedures set out in Section 12.1.4.

(e) Each Party shall bear its own counsel fees, costs, and disbursements arising out of the [***] Dispute. The costs of any Third Party expert engaged under this Section 12.1.3 will be paid by the Party against whose position the Expert's determination is made.

12.1.4. Arbitration.

(a) Subject to Section 12.2 and Section 12.1.3, any dispute, claim or controversy arising from or related in any way to this Agreement or the interpretation, application, breach, termination or validity thereof, including any claim of inducement of this Agreement by fraud or otherwise, not resolved under the provisions of Section 12.1.1, will be resolved by final and binding arbitration conducted in accordance with the terms of this Section 12.1.4(a). The arbitration will be held in New York, New York, USA according to Rules of Arbitration of the ICC. The arbitration will be conducted by a panel of three arbitrators with significant experience in the pharmaceutical industry, unless otherwise agreed by the Parties, appointed in accordance with applicable ICC rules. Any arbitration herewith will be conducted in the English language to the maximum extent possible. The arbitrators will render a written decision no later than six months following the selection of the arbitrators, including a basis for any damages awarded and a statement of how the damages were calculated. Any award will be promptly paid in U.S. dollars free of any tax, deduction or offset. Each Party agrees to abide by the award rendered in any arbitration conducted pursuant to this Section 12.1.4. With respect to money damages, nothing contained herein will be construed to permit the arbitrator or any court or any other forum to award punitive or exemplary damages, except in the case of breach of ARTICLE 11. By entering into this agreement to arbitrate, the Parties expressly waive any claim for punitive or exemplary damages, except in the case of breach of ARTICLE 11. Each Party will pay its legal fees and costs related to the arbitration (including witness and expert fees). Judgment on the award so rendered will be final and may be entered in any court having jurisdiction thereof.

(b) EACH PARTY HERETO WAIVES ITS RIGHT TO TRIAL OF ANY ISSUE BY JURY. EACH PARTY HERETO WAIVES ANY CLAIM FOR ATTORNEYS' FEES AND COSTS AND PREJUDGMENT INTEREST FROM THE OTHER.

12.1.5. **Court Actions**. Nothing contained in this Agreement will deny either Party the right to seek injunctive or other equitable relief from a court of competent jurisdiction in the context of a *bona fide* emergency or prospective irreparable harm, and such an action may be filed and maintained notwithstanding any ongoing dispute resolution discussions or arbitration proceeding. In addition, either Party may bring an action in any court of competent jurisdiction to resolve disputes pertaining to the validity, construction, scope, enforceability, infringement or other violations of patents or other proprietary or intellectual property rights, and no such claim will be subject to arbitration pursuant to Section 12.1.4.

12.2. Governing Law; Jurisdiction; Equitable Relief; Losses; Remedies.

12.2.1. This Agreement will be governed by and construed and enforced in accordance with the laws of the State of New York, USA, without reference to any rules of conflicts of laws. For clarification, any dispute relating to the scope, validity, enforceability or infringement of any Patents will be governed by and construed and enforced in accordance with the patent laws of the applicable jurisdiction.

12.2.2. Each Party acknowledges and agrees that the restrictions set forth in Section 3.1 of this Agreement are reasonable and necessary to protect the legitimate interests of the other Party and that the other Party would not have entered into this Agreement in the absence of such restrictions, and that any breach or threatened breach of any of these provisions will probably result in irreparable injury to the other Party for which there will be no adequate remedy at law. In the event of a breach or threatened breach of any such provision, each Party will be authorized and entitled to obtain from any court of competent jurisdiction equitable relief, whether preliminary or permanent, specific performance and an equitable accounting of all earnings, profits and other benefits arising from such breach, which rights will be cumulative and in addition to any other rights or remedies to which such Party may be entitled in law or equity. Each Party agrees to waive any requirement that the other Party (a) post a bond or other security as a condition for obtaining any such relief, and (b) show irreparable harm, balancing of harms, consideration of the public interest or inadequacy of monetary damages as a remedy. Nothing in this Section 12.2.2 is intended, or should be construed, to limit a Party's rights to equitable relief or any other remedy for a breach of any other provision of this Agreement. Except for (i) the offsets and credits explicitly set forth in Section 6.6, Section 6.8.3(b), Section 6.8.4(b), Section 6.11 and Section 10.3.3(b)(ii), (ii) any amount awarded to be paid by one Party to the other by the panel of arbitrators in a final and binding arbitration proceeding adjudicated under Section 12.1.4(a), and (iii) any offset of undisputed but unpaid amounts under this Agreement, neither Party will have the right to set off any amount it is owed or believes it is owed against payments due or payable to the other Party under this Agreement.

12.2.3. Neither Party will be entitled to recover any Losses relating to any matter arising under one provision of this Agreement to the extent that such Party has already recovered Losses with respect to such matter pursuant to other provisions of this Agreement (including recoveries under Section 9.1 or Section 9.2, and the offsets under Section 6.8.4(b)).

12.2.4. Any provisions of this Agreement that describe a payment as non-refundable shall be without prejudice to either Party's right to bring a claim for breach of this Agreement, misrepresentation or any other claim permissible under Applicable Laws, including seeking recovery of payments made and damages for loss.

12.3. **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 (including with respect to a Licensed Program), without the other Party's consent, to any of its Affiliates, to any purchaser of all or substantially all of its assets to which this Agreement or relevant part relates or to any successor corporation resulting from any merger, consolidation, share exchange or other similar transaction; *provided*, if a Party transfers or assigns this Agreement (or any part hereof) to [***] described in this Agreement, then such transferring Party (or such Affiliate) ("***Transferring Party***"), will [***] due that the Transferring Party is obligated to pay to the non-transferring Party ("***Non-Transferring Party***") under ARTICLE 6 for the [***] such that the Non-Transferring Party receives [***]. In addition, Isis may assign or transfer its rights to receive payments under this Agreement (but no liabilities), without AstraZeneca's consent, to an Affiliate or to a Third Party in connection with a payment factoring transaction; *provided, however*, that Isis will provide AstraZeneca advance notice of any such proposed payment factoring transaction giving AstraZeneca a reasonable opportunity to provides comments (which Isis will consider in good faith); [***]. Any purported assignment or transfer made in contravention of this Section 12.3 will be null and void.

To the extent the Non-Transferring Party utilizes a [***] in any year, the Non-Transferring Party will [***] the Transferring Party [***] or [***]. To assist the Transferring Party in determining when [***] pursuant to the foregoing sentence, beginning with the first Annual tax return for the year in which the Transferring Party [***] payment under this Section 12.3, and each year thereafter (including, for clarity, all years in which the Non-Transferring Party [***] or [***]), the Non-Transferring Party will provide the Transferring Party with the Non-Transferring Party s' Annual tax returns (federal and state) and, in years in which the Non-Transferring Party utilizes the [***], supporting documentation for such [***].

12.4. Change of Control Event Involving AstraZeneca.

12.4.1. ***Change of Control Event – Initial Meeting***. AstraZeneca will provide written notice to Isis within [***] following the closing of a Change of Control Event involving AstraZeneca, and such notice will identify the Third Party acquiring company (the "***AstraZeneca-Acquirer***") and the contact information of the person at the AstraZeneca-Acquirer with whom Isis will work to schedule meetings between the AstraZeneca-Acquirer and Isis. Within [***] following the closing of such Change of Control Event, the AstraZeneca-Acquirer will meet with Isis at a mutually agreed date and time at Isis' facilities. Within [***] before the date of such meeting, the AstraZeneca-Acquirer will provide Isis a detailed written plan showing how the AstraZeneca-Acquirer will meet AstraZeneca's obligations under this Agreement.

12.4.2. ***Change of Control Event – Right of First Negotiation***. In the case of a Change of Control Event involving AstraZeneca, if within [***] of such Change of Control Event the AstraZeneca-Acquirer is approached by a Third Party regarding, or elects to offer a Third Party, the opportunity to acquire (by license or otherwise) rights to Develop and Commercialize a Product in [***], then the AstraZeneca-Acquirer will provide written notice to Isis together with any [***] after the date AstraZeneca exercised the applicable Collaboration Program License Right (to the extent not previously provided). Isis will then have [***] to notify the AstraZeneca-Acquirer in writing whether Isis is interested in negotiating with the AstraZeneca-Acquirer to obtain such rights to Develop and Commercialize such Product and, upon such written notice, the AstraZeneca-Acquirer and Isis will negotiate in good faith (including at least [***]) to determine mutually acceptable terms and conditions for conveying such rights to Isis. If Isis does not notify the AstraZeneca-Acquirer within such [***] period that Isis is interested in negotiating with the AstraZeneca-Acquirer to obtain the rights to Develop and Commercialize such Product, or if Isis and the AstraZeneca-Acquirer are unable to reach agreement within [***] after the AstraZeneca-Acquirer's receipt of such notice from Isis, then the AstraZeneca-Acquirer will be free to grant rights to Develop and Commercialize such Product alone or with Third Parties, *provided that* any such grant of rights made by AstraZeneca to a Third Party within [***] of the last offer to Isis shall be on terms [***].

12.4.3. ***Change of Control Event – Effect on Carryover Provisions***. In the case of a Change of Control Event involving AstraZeneca, if, within [***] after the closing of such Change of Control Event, Isis delivers written notice to AstraZeneca that Isis would like to activate the provisions of this Section 12.4.3 (an "***Activation Notice***"), then the following will apply: (i) AstraZeneca's right under Section 1.10.3(c) to restore and designate a former High Interest Target to this Agreement as a Collaboration Target and AstraZeneca's Carryover Option under Section 1.14.3 will terminate, (ii) any limitations, restrictions or obligations Isis had under Section 1.10.3(c) or related to AstraZeneca's Carryover Option under Section 1.14.3 will terminate, and (iii) any [***] or [***] (as applicable) restriction on AstraZeneca's and its Affiliate's right to Exploit ASOs under Section 1.10.3(b) and Section 1.14.3(c) will terminate.

12.5. Antitrust Filing.

12.5.1. Each Party agrees to prepare and make or cause to be prepared and made appropriate filings under the HSR Act and any other antitrust requirements relating to this Agreement and the transactions contemplated under this Agreement within 10 Business Days after the Execution Date. Each of the Parties agrees to cooperate in the antitrust clearance process, including by furnishing to the other Party such necessary information and reasonable assistance as the other Party may request in connection with its preparation of any filing or submission that is necessary under the HSR Act and other antitrust requirements, and to furnish promptly with the United States Federal Trade Commission ("***FTC***"), the Antitrust Division of the United States Department of Justice ("***DOJ***") and any other antitrust authority, any information reasonably requested by them in connection with such filings. Each Party shall furnish copies (subject to reasonable redactions for privilege or confidentiality concerns) of, and shall otherwise keep the other Party apprised of the status of any communications with, and any inquiries or requests for additional information from, the FTC, DOJ and any other antitrust authority, and shall comply promptly with any such inquiry or request. Each Party shall give the other Party the opportunity to review in advance, and shall consider in good faith the other Party's reasonable comments in connection with any proposed filing or communication with the FTC, DOJ or any other antitrust authority. Each Party shall consult with the other Party, to the extent practicable, in advance of participating in any substantive meeting or discussion with the FTC, the DOJ or any other antitrust authority with respect to any filings, investigation or inquiry and, to the extent permitted by such antitrust authority, give the other Party to the opportunity to attend and participate thereat. Neither Party shall withdraw its filing under the HSR Act or agree to delay the Effective Date without the prior written consent of the other Party. The Parties' rights and obligations hereunder apply only in so far as they relate to the Agreement and to the transactions contemplated under the Agreement.

12.5.2. Each Party shall use commercially reasonable efforts to obtain the expiration or early termination of the HSR Act and any other clearance required under other antitrust requirements relating to the Agreement and the transactions contemplated under the Agreement. Commercially reasonable efforts as used in this Section 12.5.2 will not include proposing, negotiating, committing to and effecting, by consent decree, hold separate order, or otherwise, (a) the sale, divestiture, disposition, licensing or sublicensing of any of a Party's or its Affiliates' assets, properties or businesses, (b) behavioral limitations, conduct restrictions or commitments with respect to such assets, properties or business, or of any of the rights or obligations of a Party under this Agreement, or (c) defending through litigation any claim asserted in court by any party that would restrain, prevent or delay the Effective Date.

(a) Other than the provisions of Section 10.1, ARTICLE 11 and ARTICLE 12 which shall apply as of the Execution Date, the rights and obligations of the Parties under this Agreement will not become effective until the waiting period under the HSR Act has been terminated or expired, or any other timeline required by another antitrust authority and there is no proceeding, order, injunction or judgment relating thereto, pending before any governmental authority in which it is sought to restrain or prohibit the transaction(s) contemplated hereby. Upon the occurrence of the Effective Date, all other provisions of this Agreement shall become effective automatically without the need for further action by the Parties.

12.5.3. Each Party shall be responsible for its fees and costs associated with the preparation and submission of any required notification and report form under the HSR Act (or to any other antitrust authority), and the provision of any supplemental information to the FTC, DOJ or other antitrust authority, including any legal fees incurred by such Party in connection with such Party's obligations pursuant to this Section 12.5.

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 facsimile transmission (receipt verified) or internationally recognized 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 AstraZeneca, addressed to:	AstraZeneca AB SE-431 83 Molndal Sweden Attention: Legal Department Fax: +46 31 7763871
with a copy to:	AstraZeneca AB Scientific Partnering and Alliances SE-431 83 Molndal Sweden Attention: Business Development Director, CVMD Fax: +46 31 7763701

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 internationally recognized overnight express courier service, the date of delivery will be deemed to be the second Business Day after such notice or request was deposited with such service. It is understood and agreed that this Section is not intended to govern the day to day business communications necessary between the parties in performing their duties, in due course, under the terms of this Agreement.

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

12.11. **Entire Agreement; Modifications**. This Agreement (including the attached Appendices, Exhibit and Schedules) sets forth and constitutes the entire agreement and understanding between the Parties with respect to the subject matter hereof, and all prior agreements, understanding, promises and representations, whether written or oral, with respect thereto are superseded hereby. Each Party confirms that it is not relying on any representations or warranties of the other Party except as specifically set forth herein. No amendment, modification, release or discharge will be binding upon the Parties unless in writing and duly executed by authorized representatives of both Parties.

12.12. **Relationship of the Parties**. It is expressly agreed that the Parties will be independent contractors of one another and that the relationship between the Parties will not constitute a partnership, joint venture or agency.

12.13. **Interpretation**. Except as otherwise explicitly specified to the contrary, (a) references to a section, appendix, exhibit or schedule means a section of, or appendix, 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 “will” and “shall” 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) references to a particular Person include such Person’s successors and assigns to the extent not prohibited by this Agreement, (f) unless otherwise specified, “$” is in reference to United States dollars, (g) 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; and (h) or the context otherwise requires, the word “or” is used in the inclusive sense (and/or).

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 generally accepted accounting principles, or in the case of non-United States sales, other applicable accounting standards, 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, Exhibit or Appendix hereto, the terms of this Agreement will apply. The Parties understand and agree that the Schedules and Appendices hereto are not intended to be the final and complete embodiment of any terms or provisions of this Agreement, and are to be updated from time to time during the Agreement Term, as appropriate and in accordance with the provisions of this Agreement.

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

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

[SIGNATURE PAGE FOLLOWS]

* - * - * - *

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

ASTRAZENECA AB (publ.)

By: */s/ Marcus Schindler*

Name: Marcus Schindler

Title: Vice President, Head of CVMD IMED

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

ISIS PHARMACEUTICALS, INC.

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

List of Appendices, Schedules and Exhibit

APPENDIX 1 – Definitions

APPENDIX 2 – Isis' Lead Candidate Checklist

APPENDIX 3 – Isis In-License Agreements

APPENDIX 4 – Isis Core Technology Patents

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SCHEDULE 1.2.1 – Preliminary Core Research Plan

SCHEDULE 1.2.2 – Preliminary Disease Research Plan

SCHEDULE 1.8 – Criteria and Activities to Achieve Target Sanction

SCHEDULE 1.13.1(a) - Draft [***] Drug Discovery Plan

SCHEDULE 1.13.1(b) – Criteria and Activities for Development Candidate Designation

SCHEDULE 1.13.2 – Isis' Development Pipeline as of the Execution Date

SCHEDULE 2.1.1 – JSC Governance

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SCHEDULE 2.8 – Bioethics Policy

SCHEDULE 5.1.1 – Specific Performance Milestone Events

SCHEDULE 5.5.1 – Isis' Fully Absorbed Cost of Goods Methodology

EXHIBIT 1 – AstraZeneca 5R Framework

APPENDIX 1

DEFINITIONS

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

"$" means the lawful currency of the United States.

"***Acceptance of Filing***" means, with respect to an NDA, MAA, JNDA, CNDA or BDRP 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 AstraZeneca, its Affiliate or Sublicensee of written notice of validation by the EMA of such MAA 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 of Filing will be determined upon the validation of such MAA by the applicable Regulatory Authority in a Major Market in the EU, (c) in Japan, receipt by AstraZeneca, its Affiliate or Sublicensee 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), (c) in China, receipt by AstraZeneca, its Affiliate, or Sublicensee, of written notice of acceptance of filing of such CNDA from the relevant regulatory authority in China (i.e., the China Food and Drug Administration or the provincial-level food and drug regulatory authority, as law and regulation may require, or any successor agencies thereto), and (d) in Brazil, the receipt by AstraZeneca, its Affiliate or Sublicensee of written notice from the Brazilian National Health Surveillance Agency (ANVISA) (or any successor agencies thereto) confirming that the BDRP has been received.

"***Acquiring Party***" has the meaning set forth in Section 3.3.1.

"***Activation Notice***" has the meaning set forth in Section 12.4.3.

"***Additional Core IP***" has the meaning set forth in Section 6.8.3(a).

"***Additional Product-Specific Patents***" has the meaning set forth in Section 6.8.2(b)(1).

"***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 at the applicable time during the Term. 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.

"***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 2.2.

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

"***Anti-Corruption Laws"*** means the U.S. Foreign Corrupt Practices Act, as amended, the UK Bribery Act 2010, as amended, and any other applicable anti-corruption laws and laws for the prevention of fraud, racketeering, money laundering or terrorism.

"***API***" means the bulk active pharmaceutical ingredient manufactured in accordance with cGMP (unless expressly stated otherwise) for a Product. The quantity of API will be the as-is gross mass of the API after lyophilization (i.e., including such amounts of water, impurities, salt, heavy, metals, etc. within the limits set forth in the API specifications) and before release, retention, stability or characterization samples are removed (if needed).

"***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 (i) with respect to a Product in the EU, approval from the applicable Regulatory Authority in at least one member state in the EU sufficient for the manufacture, distribution, use, marketing and sale of such Product and either (x) pricing approval in such jurisdiction in accordance with Applicable Laws has been obtained, or (y) the first commercial sale of a Product in the EU has occurred; and (ii) with respect to a Product in any regulatory jurisdiction other than the EU, approval sufficient for the manufacture, distribution, use, marketing and sale of such Product in such jurisdiction in accordance with Applicable Laws.

"***Approval by AstraZeneca's Internal Decision Body to Initiate a Phase 3 Study***" means, with respect to a Product, that the internal governing body within AstraZeneca responsible for authorizing the commencement of a Phase 3 Study, has granted such authorization to commence such a Phase 3 Study.

"***ASO***" means a single-stranded or double-stranded oligonucleotide compound, or analog, variant, mimic, or mimetic thereof, having a sequence that is between six and one hundred nucleotides long and is designed to hybridize to a nucleic acid transcript via the binding, partially or wholly, of such compound to the nucleic acid transcript.

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

"***AstraZeneca-Acquirer***" has the meaning set forth in Section 12.4.

"***AstraZeneca Background Intellectual Property***" means any Know-How and Patent Rights that: (i) were Controlled by AstraZeneca prior to the Effective Date; and/or (ii) are Controlled by AstraZeneca on or after the Effective Date that were not created or acquired in connection with performance of any Collaboration Plan and/or in connection with the Exploitation of a Product, which Patents and Know-How are necessary to Develop, Manufacture or Commercialize a Product in the Field.

"***AstraZeneca Collaboration Intellectual Property***" means any Know-How and Patent Rights that were discovered, developed, invented or created in connection with the performance of any Collaboration Plan by or on behalf of AstraZeneca, including AstraZeneca's interest in any Jointly-Owned Collaboration Technology.

"***AstraZeneca Conducted Activities***" means, under a Collaboration Plan, any and all Research, pre-clinical and/or clinical activities that are not Isis Conducted Activities.

"***AstraZeneca Field***" means [***].

"***AstraZeneca Full Royalty***" has the meaning set forth in Section 6.7.1.

"***AstraZeneca Indemnitees***" has the meaning set forth in Section 9.2.

"***AstraZeneca Know-How***" means any Know-How owned, used, developed by, or licensed to AstraZeneca or its Affiliates (other than from Isis pursuant to this Agreement), in connection with AstraZeneca's performance of its obligations under this Agreement, in each case to the extent Controlled by AstraZeneca or its Affiliates at any time during the Agreement Term that is necessary to Develop, Manufacture or Commercialize a Product in the Field and such Know-How does not constitute AstraZeneca Background Intellectual Property.

"***AstraZeneca Patents***" means any Patent Rights owned, used, developed by, or licensed to AstraZeneca or its Affiliates (other than from Isis pursuant to this Agreement) that are invented by AstraZeneca or its Affiliates or licensors in connection with AstraZeneca's performance of its obligations under this Agreement, in each case to the extent Controlled by AstraZeneca or its Affiliates at any time during the Agreement Term that is necessary to Develop, Manufacture or Commercialize a Product in the Field and such patents do not constitute AstraZeneca Background Intellectual Property.

"***AstraZeneca Product-Specific Patents***" means all Product-Specific Patents owned, used, created, developed by, or licensed to AstraZeneca or its Affiliates (other than from Isis pursuant to this Agreement) (i) as of the Effective Date, or (ii) arising at any time during the Agreement Term, in each case to the extent (x) Controlled by AstraZeneca or its Affiliates in connection with performance of obligations under this Agreement, and (y) such Product-Specific Patents do not constitute AstraZeneca Background Intellectual Property.

"***AstraZeneca-Prosecuted Patents***" has the meaning set forth in Section 7.2.4(b).

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

"***AstraZeneca Technology***" means AstraZeneca's interest in AstraZeneca Collaboration Intellectual Property, AstraZeneca Product-Specific Patents, AstraZeneca Know-How, AstraZeneca Patents, including AstraZeneca Background Intellectual Property, and any trademarks described in Section 4.1.6, owned, used, developed by, or licensed to AstraZeneca or its Affiliates (other than from Isis pursuant to this Agreement) that are necessary or used by AstraZeneca to Develop, Manufacture or Commercialize a Product.

"***Audit***" has the meaning set forth in Section 9.7.6.

"***Audit Report***" has the meaning set forth in Section 6.11.

"***Bankruptcy Code***" has the meaning set forth in Section 10.2.6(b).

"***BDRP***" means a drug registration petition filed with the Brazilian National Health Surveillance Agency (ANVISA) after completion of any necessary Clinical Studies to obtain Approval to market a Product in Brazil.

"***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, US and London, England are open for business.

"***Calendar Quarter***" means a period of three consecutive calendar 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 2015, the Effective Date) and ending on December 31.

"***Candidate Drug***" means a Compound nominated for further development by AstraZeneca in accordance with AstraZeneca's internal processes.

"***Candidate Failure Date***" has the meaning set forth in Section 1.14.3.

"***Cardiovascular Disease***" means [***].

"***Carryover Option***" has the meaning set forth in Section 1.14.3(e)(ii).

"***Carryover Period***" has the meaning set forth in Section 1.14.3(d).

"***CDA***" has the meaning set forth in Section 11.2.

"***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 Event***" means any (a) direct or indirect acquisition of all or substantially all of the assets of a Party, (b) direct or indirect acquisition by a Person, or group of Persons acting in concert, of [***]% or more of the voting equity interests of a Party, (c) tender offer or exchange offer that results in any Person, or group of Persons acting in concert, beneficially owning [***]% or more of the voting equity interests of a Party, or (d) merger, consolidation, other business combination or similar transaction involving a Party, pursuant to which any Person owns all or substantially all of the consolidated assets, net revenues or net income of a Party, taken as a whole, or which results in the holders of the voting equity interests of a Party immediately prior to such merger, consolidation, business combination or similar transaction ceasing to hold [***]% or more of the combined voting power of the surviving, purchasing or continuing entity immediately after such merger, consolidation, other business combination or similar transaction, in all cases where such transaction is to be entered into with any Person other than the other Party to this Agreement or its Affiliates.

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

"***Clinical Study***" or "***Clinical Studies***" means a Phase 1 Study, Phase 2 Study, Phase 2b Study, Phase 3 Study, 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, JNDA or other similar marketing application.

"***CNDA"*** means the Chinese equivalent of an NDA filed with the China Food and Drug Administration or provincial-level food and drug regulatory authority, as law and regulation may require, or any successor agency thereto.

"***CMO***" means a Third Party primarily engaged in providing contract manufacturing or services and is not primarily engaged in drug discovery, development or commercialization of ASOs as pharmaceutical products.

"***Collaboration Plan***" means (i) the Core Research Plan, (ii) the Disease Research Plan, or (iii) any Drug Discovery Plan including the [***] Drug Discovery Plan.

"***Collaboration Program***" means a discovery research program focused on discovering and optimizing at least one ASO designed to bind to the Collaboration Target that is suitable for selection as Development Candidate in accordance with the applicable Drug Discovery Plan.

"***Collaboration Program Exercise Date***" has the meaning set forth in Section 1.16.3.

"***Collaboration Program License Right***" has the meaning set forth in Section 1.16.

"***Collaboration Program License Right Deadline***" has the meaning set forth in Section 1.16.

"***Collaboration Program Term***" has the meaning set forth in Section 1.13.3.

"***Collaboration Target***" means (i) [***], or (ii) any High Interest Targets that are designated under Section 1.10 to be the subject of a Collaboration Program (and thereafter if AstraZeneca exercises its Collaboration Program License Right with respect to such High Interest Target).

"***Commercialize***," "***Commercialization***" or "***Commercializing***" means any and all activities directed to marketing, promoting, detailing, distributing, importing, having imported, exporting, having exported, holding, transporting, selling or offering to sell a Product following receipt of Approval for the Product in the applicable country, including conducting pre-and post-Approval activities, including studies reasonably required to increase the market potential of the Product and studies to provide improved formulation and Product delivery, and launching and promoting the Product in each country.
"***Commercializing Party***" means (a) AstraZeneca, with respect to a Product that is being Developed and Commercialized by or on behalf of AstraZeneca, its Affiliates or Sublicensees hereunder, and (b) Isis, with respect to a Discontinued Product that is being Developed and Commercialized by or on behalf of Isis, its Affiliates or Sublicensees hereunder.

"***Commercially Reasonable Efforts***" with respect to:

(a) AstraZeneca means that level of efforts and resources, at the relevant point in time, commonly used in the pharmaceutical industry for a product of similar commercial potential and in a similar commercial space at a similar stage in its lifecycle, taking into consideration relative safety and efficacy, product profile, the competitiveness of the marketplace, market potential, the relative profitability of the product (including pricing and reimbursement status) and other relevant factors, including technical, legal, scientific and/or medical factors.

(b) Isis means the level of efforts and resources, at the relevant time, that, consistent with Isis' normal practices, Isis would dedicate to an activity when it is seeking to achieve the particular result in a similar timeframe for its own benefit. Without limiting any of the foregoing, Commercially Reasonable Efforts as it applies to Isis' Research or Development of a Product hereunder includes use of Commercially Reasonable Efforts to perform the Isis Conducted Activities under each Collaboration Plan in accordance with the timelines set forth therein.

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

"***Competitive ASO***" has the meaning set forth in Section 3.3.

"***Complete***," "***Completed***," or "***Completion***" means[***].

"***Compound***" means any ASO that is designed to bind to a Collaboration Target, where such ASO is discovered by Isis prior to the date on which such Target becomes a High Interest Target (or, with respect to [***], the Effective Date), or in the performance of a Collaboration Plan; and in each case any salt, hydrate, solvate or pro-drug thereof. For clarity, ASOs will be different Compounds if they have different sequences of nucleotides, use different modified nucleotides (including a different backbone, sugar moiety or base modification), or if they employ different Conjugate Technology, such as GalNAc.

"***Confidential Information***" means any confidential or proprietary information or materials, patentable or otherwise, in any form (written, oral, photographic, electronic, magnetic, or otherwise) which is disclosed by the Disclosing Party or otherwise received or accessed by the 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. "*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.

"***Conjugate Technology***" means chemistry designed to enhance targeting and/or uptake of antisense drugs to specific tissues and cells. Conjugate Technology includes N-acetylgalactosamine (GalNAc) ligand conjugates capable of binding to the asialoglycoprotein receptor (ASGP-R) and enhancing the targeting and/or uptake of antisense drugs to the liver.

"***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 in the case of a license to AstraZeneca, Isis Supported Pass-Through Costs or AstraZeneca Supported Pass-Through Costs), 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.

"***Core Research Term***" has the meaning set forth in Section 1.3.1.

"***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.

"***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 a Product to seek Approval for additional indications for such Product, including importing, having imported, exporting, having exported, holding and transporting in connection with any activities prior to Approval.

"***Development Candidate***" means, with respect to a Collaboration Program, a Compound that meets the Development Candidate Success Criteria or is otherwise designated by AstraZeneca under Section 1.14.1 (or, with respect to [***], designated by the Expert in accordance with Section 12.1.3).

"***Development Candidate Success Criteria***" means the success criteria for a development candidate for such program as set out in the applicable Drug Discovery Plan. Unless otherwise agreed by the JSC such success criteria will include the items set out in the checklist Isis uses as of the Effective Date when reviewing potential development candidates for approval as attached hereto as Appendix 2.

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

"***Discontinued Product***" has the meaning set forth in Section 10.3.1.

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

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

"***Disease Research Term***" has the meaning set forth in Section 1.3.2.

[***]

"***DOJ***" means the Antitrust Division of the United States Department of Justice.

"***Drug Discovery Plan***" means any drug discovery plan for a Collaboration Program focused on a particular Collaboration Target as amended from time to time in accordance with this Agreement.

"***Effective Date***" means the date that all necessary authorizations, consents, orders or approval of, or declarations or filings with, or expirations of waiting periods under the HSR Act, as applicable to the consummation of the transactions contemplated by this Agreement, have been received, authorized, permitted or expired.

"***Eligible Target***" has the meaning set forth in Section 1.5.

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

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

"***Evaluation Period***" has the meaning set forth in Section 1.16.1.

"***Exclusion Criteria***" has the meaning set forth in Section 1.6.

"***Exclusive Target***" means (i) any Reserved Target, (ii) High Interest Target, or (iii) any Collaboration Target. The term "***Exclusive Targets***" means collectively the Reserved Targets, the High Interest Targets and the Collaboration Targets.

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

"***Exploit***" means to Research, Develop, Manufacture and Commercialize and "***Exploiting***" and "***Exploitation***" have corresponding meanings. For purposes of this Agreement, references to the term "*Exploit*" in the context of non-Compounds and non-Products will be read to include the list of activities in the definition of "*Exploit*" (and the relevant supporting defined terms) *mutatis mutandis*.

"***Failed Candidate***" has the meaning set forth in Section 1.14.3(a).

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

"***Field***" means (i) with respect to the practice of the Isis Core Technology Patents and the Isis Manufacturing and Analytical Patents, the prophylactic or therapeutic use or form of administration in humans or animals of Product for any indication, (ii) with respect to the practice of the Isis Product-Specific Patents, the prophylactic, therapeutic or diagnostic use or form of administration in humans or animals of a Product for any indication; and (iii) in all other cases, the prophylactic, therapeutic or diagnostic use or form of administration in humans or animals of a product for any indication.

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

"***FTC***" means the Antitrust Division of the United States Department of Justice.

"***FTE***" means the efforts of one or more employees of Isis equivalent to the efforts of one full-time Isis employee for one year, or in the case of less than a full-time dedicated person, a full-time equivalent person-year based upon a total of one thousand seven hundred and ten (1710) hours per year of work on the development program.
"***FTE Rate***" means [***].

"***Fully Absorbed Cost of Goods***" means the costs incurred by Isis as determined using the methodology set forth in SCHEDULE 5.5.1 fairly applied and as employed on a consistent basis throughout Isis' operations.

"***Government Official***" means any Person employed by or acting on behalf of a government, government-controlled entity or public international organization; any political party, party official or candidate; any Person who holds or performs the duties of an appointment, office or position created by custom or convention; and any Person who hold himself out to be the authorized intermediary of any of the foregoing.

"***High Interest Target***" has the meaning set forth in Section 1.7.1(a).

"***High Interest Target List***" has the meaning set forth in Section 1.7.1(a).

"***HSR Act***" means the United States Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended from time to time.

"***ICC***" has the meaning set forth in Section 12.1.3(b).

"***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, including API manufacturing to support such activities.

"***Indemnification Claim Notice***" has the meaning set forth in Section 9.3.

"***Indemnified Party***" has the meaning set forth in Section 9.3.

"***Indication***" means [***].

"***Indirect Taxes***" means value added taxes, sales taxes, consumption taxes and other similar taxes required by law to be disclosed on the invoice.

"***Initiation***" or "***Initiate***" means, with respect to any Clinical Study, dosing of the first human subject in such Clinical Study.

"***Integrated Product Plan***" or "***IPP***" has the meaning set forth in Section 5.1.2.

"***IP Managers***" has the meaning set forth in Section 7.1.5(a).

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

"***Isis Background Intellectual Property***" means any Know-How and Patent Rights that: (i) were Controlled by Isis prior to the Effective Date; and/or (ii) are Controlled by Isis on or after the Effective Date that were not created or acquired in connection with performance of any Collaboration Plan and/or in connection with the Exploitation of a Product, in each case which Patents and Know-How are necessary to practice Isis Collaboration Intellectual Property.

"***Isis Collaboration Intellectual Property***" means any Know-How and Patent Rights that were discovered, developed, invented or created in connection with the performance of any Collaboration Plan by or on behalf of Isis, including Isis' interest in any Jointly-Owned Collaboration Technology.

"***Isis Conducted Activities***" means the Research and Development activities for which Isis is designated as responsible under any Collaboration Plan.

"***Isis Core Technology Patents***" means all Patent Rights owned, used, developed by, or licensed to Isis or its Affiliates (other than from AstraZeneca pursuant to this Agreement), 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 APPENDIX 4 attached hereto.

"***Isis Field***" means [***].

"***Isis In-License Agreements***" means any agreement listed in APPENDIX 3 as may be updated in accordance with Section 6.8.5 or otherwise with AstraZeneca's written consent.

"***Isis Indemnitees***" has the meaning set forth in Section 9.1.

"***Isis Internal ASO Safety Database***" has the meaning set forth in Section 5.4.

"***Isis Know-How***" means any Know-How, including Isis' interest in any Jointly-Owned Collaboration Know-How, owned, used, developed by, or licensed to Isis or its Affiliates (other than from AstraZeneca pursuant to this Agreement), in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term that is necessary or useful to Develop, Manufacture or Commercialize a Product in the Field. Isis Know-How does not include the Isis Manufacturing and Analytical Know-How.

"***Isis Manufacturing and Analytical Know-How***" means Know-How, including Isis' interest in any Jointly-Owned Collaboration 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 (other than from AstraZeneca pursuant to this Agreement), 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 Isis' interest in any Jointly-Owned Collaboration 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 (other than from AstraZeneca pursuant to this Agreement), in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term. A list of Isis Manufacturing and Analytical Patents as of the Effective Date is set forth on APPENDIX 5 attached hereto. Isis Manufacturing and Analytical Patents do not include the Isis Product-Specific Patents or the Isis Core Technology Patents.

"***Isis Product-Specific Patents***" means all Product-Specific Patents, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term. A list of Isis Product-Specific Patents as of the Effective Date is set forth on APPENDIX 6 attached hereto.

"***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).

"***Jointly-Owned Collaboration Know-How***" means Know-How discovered, developed, invented or created jointly in the performance of a Collaboration Plan by or on behalf of both Parties or their respective Affiliates or Third Parties acting on their behalf that is necessary or useful to Develop, Manufacture or Commercialize a Product in the Field.

"***Jointly-Owned Collaboration Patents***" means any Patent Rights that claim or cover Jointly-Owned Collaboration Know-How.

"***Jointly-Owned Collaboration Technology***" means Jointly-Owned Collaboration Know-How and Jointly-Owned Collaboration Patents.

"***Kidney Disease***" means [***].

"***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, and in each case that are not Covered by an issued Patent Right.

"***Knowledge***" means the good faith, actual understanding of the facts and information by a Party's or any of its Affiliate's executive officers and their attorneys employed in their Legal Department and Patent Department as of the Effective Date or a Bring-Down Date (as applicable); *provided that*, with respect to information regarding the status of Patent Rights or other intellectual property rights, "*Knowledge*" means the good faith, actual understanding of the facts and information by a Party's or any of its Affiliate's executive officers and their attorneys employed in their Legal Department and Patent Department as of the Effective Date or a Bring-Down Date (as applicable) after performing a diligent investigation with respect to such facts and information as is customary in the conduct of its business with respect to such Patent Rights or other intellectual property rights (and not, for clarity, a diligent investigation solely in connection with this Agreement).

"***Lead Candidate****"* means, in the case of a Collaboration Program, the Compound identified by Isis as being the lead candidate for such program.

"***Lead Candidate Data Package***" means, with respect to a Collaboration Program, [***].

"***Lead Compounds***" has the meaning set forth in Section 1.14.1.

"***Licensed CMO***" has the meaning set forth in Section 4.1.2(a)(ii).

"***Licensed Know-How***" means Isis Manufacturing and Analytical Know-How, and Isis Know-How. For clarity, at the Execution Date Licensed Know-How does not include any Know-How covering formulation technology or delivery devices unless such Know-How is included in the Jointly-Owned Collaboration Know-How.

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

"***Licensed Program***" means a Collaboration Program following exercise of the applicable Collaboration Program License Right for so long as the license under Section 4.1.1 for such program is effective.

"***Licensed Technology***" means any and all Licensed Patents, Licensed Know-How, and any trademarks described in Section 4.1.6, to the extent necessary or useful to Research, Develop, Manufacture or Commercialize a Product in the Field.

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

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

"***MAA Approval***" means the grant of a marketing authorization by the European Commission for a Product in the European Union.

"***Major Market***" means any of the following countries: [***].

"***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, importing and keeping, for pre-clinical and clinical purposes, of API or a Product in finished form.

"***Material Anti-Corruption Law Violation"*** means a violation of an Anti-Corruption Law relating to the subject matter of this Agreement which would if it were publicly known, in the reasonable view of AstraZeneca, have a material adverse effect on Isis or on the reputation of AstraZeneca because of its relationship with Isis.

"***Metabolic Disorder***" means [***].

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

"***MSA***" has the meaning set forth in Section 5.5.2.

"***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.

"***Net Sales***" means the gross invoiced amount on sales of Products by or on behalf of AstraZeneca, its Affiliates, and its Sublicensees to Third Parties (which Third Parties will include Distributors) after deduction of the following amounts, to the extent taken:

(a) normal and customary trade, quantity or prompt settlement discounts (including initial launch stocking discounts, chargebacks and allowances) actually allowed;

(b) amounts repaid or credited by reason of rejection, returns or recalls of goods, rebates or *bona fide* price reductions determined by AstraZeneca, its Affiliates or its Sublicensees in good faith;

(c) rebates and similar payments made with respect to sales paid for by any governmental or Regulatory Authority such as, by way of illustration and not in limitation of the Parties' rights hereunder, Federal or state Medicaid, Medicare or similar state program in the United States or equivalent governmental program in any other country;

(d) any invoiced amounts which are not collected by AstraZeneca, its Affiliates or its Sublicensees, including bad debts;

(e) excise taxes, value added taxes, sales taxes, consumption taxes and other similar taxes (excluding any income, franchise or withholding taxes), customs duties, customs levies and import fees imposed on the sale, importation, use or distribution of the Products, including fees paid pursuant to Section 9008 of the Patient Protection and Affordable Care Act that AstraZeneca, its Affiliates or its or their Sublicensees, as applicable, allocable to sales of such Products in accordance with AstraZeneca's, its Affiliates' or its or their Sublicensees' standard policies and procedures consistently applied across its products, as applicable;

(f) the portion of administrative fees paid during the relevant time period to group purchasing organizations or pharmaceutical benefit managers relating to such Products;

(g) service fees payable under any wholesaler agreement, distribution services agreement, inventory management agreement or other similar agreement;

(h) any other similar and customary deductions (including co-pay cards) that are consistent with the United States generally accepted accounting principles or, in the case of non-United States sales, other applicable accounting standards;

(i) an allowance for transportation costs, distribution expenses, special packaging and related insurance charges equal to [***] ([***]) of the amount arrived at after application of the deductions under clauses (a) to (h) above; and

(j) the actual cost paid by AstraZeneca, its Affiliates or Sublicensees for each unit of a Device.

Net Sales (including any deductions) will be calculated using AstraZeneca's internal audited systems used to report such sales as adjusted for any of the items above not taken into account in such systems, and in each case which are in accordance with generally accepted accounting principles, fairly applied and as employed on a consistent basis throughout AstraZeneca's operations. Deductions pursuant to subsection (d) above will be taken in the Calendar Quarter in which such sales are no longer recorded as a receivable. As used above, the term *"Device"* means any device approved by a Regulatory Authority for use with a Product that is necessary to administer the Product to a patient (i.e. without such device the Product cannot be delivered in accordance with the Approval).

If a Product is sold as part of a Combination Product (as defined below), the Net Sales from such Product, for the purposes of determining royalty payments, will be determined by multiplying the Net Sales (as determined without reference to this paragraph) of the Combination Product by the fraction A/(A+B), where A is the standard sales price of the ready-for-sale form of the Product, containing the same amount of Compound as the sole active ingredient as the Combination Product in question, in the given country when sold separately in finished form; and B is the standard sales price of the ready-for-sale form of the product containing the same amount of the other therapeutically active ingredient(s) that is contained in the Combination Product in question, in the given country, each during the applicable royalty period or, if sales of all compounds did not occur in such period, then in the most recent royalty reporting period. In the event, however, that if, in a specific country either or both of the Compound and the other therapeutically active ingredient in such Combination Product are not sold separately in such country, a market price for such Product and such other active ingredient will be negotiated by the Parties in good faith for the purposes of performing the calculation above to determine royalty payments on the Net Sales from such Combination Product. As used above, the term ***"Combination Product"*** means a Product that includes at least one additional therapeutically active ingredient (whether coformulated or copackaged) and is not a Compound.

"***New Third Party Compound Technology***" has the meaning set forth in Section 1.13.2.

[***]

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

"***Non-Transferring Party***" has the meaning set forth in Section 12.3.

"***Other Leads***" has the meaning set forth in Section 1.14.1.

"***Party***" or "***Parties***" means AstraZeneca and Isis individually or collectively.

"***Party Representatives***" has the meaning set forth in Section 9.7.1.

"***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).

"[***]" means the gene, [***].

"[***] ***Carryover Option***" means a Carryover Option exercised with respect to [***].

"[***] ***CD Milestone***" has the meaning set forth in Section 6.3.

"[***] ***Compound***" means any ASO that is designed to bind to [***], where such ASO is (i) discovered by Isis prior to the Effective Date, or (ii) discovered by Isis in the performance of the [***] Program. For clarity, ASOs will be different Compounds if they have different sequences of nucleotides, use different modified nucleotides (including a different backbone, sugar moiety or base), or if they employ different Conjugate Technology, such as GalNAc.

"[***] ***Drug Discovery Plan***" means the drug discovery plan for the [***] Program (a draft of which is attached hereto as SCHEDULE 1.13.1(a)) to be adopted by the JSC and thereafter as updated by the JSC from time to time in accordance with this Agreement.

"[***] ***Program***" means the Research and/or Development program for [***] Products under this Agreement.

"[***] ***Product***" means each [***] Compound and any product containing such [***] Compound as an active pharmaceutical ingredient (including any salt, hydrate, solvate or pro-drug thereof).

"[***] ***Program***" means the drug discovery program for [***] Products under this Agreement.

"[***] ***Success Criteria***" means the Development Candidate Success Criteria for the [***] Program as set out in the [***] Drug Discovery Plan.

"***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 as a contract manufacturer, 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 Product; and (2) material transfer agreements with academic collaborators or non-profit institutions in connection with the Isis Conducted Activities approved by AstraZeneca, such approval not to be unreasonably withheld or delayed.

"***Person***" means 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.

"***Phase 1 Study***" means the first clinical study conducted in humans. "*Phase 1 Study*" includes any clinical study designated under an IPP as a "*Phase 1 Study", "Phase 1(a) Study",* "*Phase 1 Trial*", or "*Phase 1a Trial*".

"***Phase 2 Study***" means the first clinical study where the protocol anticipates that a patient participating in the study will be administered Product for more than eight weeks. For clarity, the continuation of treatment of patients for more than eight weeks in an open label arm of a Phase 1(b) Study will not result in that study being deemed to be a Phase 2 Study. "*Phase 2 Study*" includes any clinical study designated under an IPP as a "*Phase 2 Study,*" "*Phase 2a Study*," *Phase 2b Study*," "*Phase 2 Trial*," *Phase 2a Trial*" or "*Phase 2b Trial*".

"***Phase 2b Study***" means a further Phase 2 Study for a Product for the same Indication that is intended to identify the definite dose range for efficacy at the primary endpoint for that Indication.

"***Phase 3 Study***" means a clinical study in humans performed to gain evidence of statistical significance of the efficacy of a Product in a target patient population, and to obtain expanded evidence of safety for such Product that is needed to evaluate the overall benefit-risk relationship of such Product and provide an adequate basis for obtaining Regulatory Approval, including physician labeling, as described in 21 C.F.R. 312.21(c), or its equivalent outside the United States. "*Phase 3 Study*" includes any clinical study designated under an IPP as a "*Phase 3 Study,*" "*Phase 3 Trial*," "*Pivotal Study*" or "*Registration Study*."

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

"***Primary Diseases***" has the meaning set forth in the Recitals. "*Primary Diseases*" does not include any neurology diseases or ocular diseases associated with a Primary Disease (e.g., diabetic retinopathy).

"***Prior Agreements***" means the agreements listed on APPENDIX 7 attached hereto.

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

"***Product***" means (i) each Compound and any product containing such Compound as an active pharmaceutical ingredient (including any salt, hydrate, solvate or pro-drug thereof), or (ii) a [***] Product.

"***Product-Specific Patents***" means Patent Rights Controlled by a Party or any of its Affiliates on or after the Effective Date claiming: (i) the specific composition of matter of a Product, or (ii) methods of using such a Product as a prophylactic, therapeutic or diagnostic.

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

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

"***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 regulating or otherwise exercising authority with respect to the Development, Manufacture, marketing, sale or other Commercialization of a Product in any country.

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

"***Release Notice***" means a written notice delivered by AstraZeneca to Isis within [***] after the Target Failure Date or Candidate Failure Date (as applicable), pursuant to which AstraZeneca releases Isis from any obligation to restore a former High Interest Target or a former Collaboration Target (together with ASOs designed to bind to such former High Interest Target or former Collaboration Target) to the Collaboration pursuant to Sections 1.10.3(c) or 1.14.3(e).

"***Relevant Authority***" means any court or government body, whether national, supra-national, federal, state, local, foreign or provincial, including any political subdivision thereof, including any department, commission, board, bureau, agency, or other regulatory or administrative governmental authority or instrumentality, and further including any quasi-governmental Person or entity exercising the functions of any of these.

"***Research***" means conducting research activities with Compounds, 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 Collaboration***" means the conduct of the Disease Research Program, the Core Research Program and the Collaboration Programs in accordance with this Agreement.

"***Reserved Target***" has the meaning set forth in Section 1.7.

"***Reserved Target List***" has the meaning set forth in Section 1.7.

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

"***Royalty Period***" has the meaning set forth in Section 6.7.2(a).

"***Senior Representatives***" has meaning set forth in Section 12.1.1.

"***Service Provider***" means the Third Party(ies) conducting the original and revised studies under a Collaboration Plan.

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

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

"***Target***" means any (i) pre-mRNA or mRNA of a gene target, and/or (ii) non-coding RNA.

"***Target Failure Date***" has the meaning set forth in Section 1.10.3.

"***Target Sanction***" means [***].

"***Target Sanction Data Package***" means, with respect to a High Interest Target, [***].

"***Terminated Program***" has the meaning set forth in Section 10.3.1.

"***Terminated Target***" has the meaning set forth in Section 10.3.1.

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

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

"***Third Party Obligations***" means any financial and non-financial encumbrances, obligations, restrictions, or limitations imposed by an agreement between a Party and a Third Party that relate to a Product or an Exclusive Target, including field or territory restrictions, covenants, milestone payments, diligence obligations, sublicense revenue, royalties, or other payments.

"***Transferring Party***" has the meaning set forth in Section 12.3.

[***]

"***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.

"***Work Plan Reports***" has the meaning set forth in Section 2.7.

APPENDIX 2
Isis' Lead Candidate Checklist

[***]

APPENDIX 3

Isis In-License Agreements

[***]

APPENDIX 4

Isis Core Technology Patents

[***]

APPENDIX 5

Isis Manufacturing and Analytical Patents

[***]

APPENDIX 6

Isis Product-Specific Patents

(RELEVANT TO [***])

[***]

APPENDIX 7

Prior Agreements

[***]

SCHEDULE 1.2.1

Preliminary Core Research Plan

[***]

SCHEDULE 1.2.2

Outline for Preliminary Disease Research Plan

[***]

SCHEDULE 1.8

Criteria and Activities to Achieve Target Sanction

[***]

SCHEDULE 1.13.1(a)

Draft [***] Drug Discovery Plan

[***]

SCHEDULE 1.13.1(b)

Criteria and Activities for Development Candidate Designation

[***]

SCHEDULE 1.13.2

Isis' Development Pipeline as of the Execution Date

SCHEDULE 2.1.1

JSC GOVERNANCE

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

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

(b) The co-chairs will be responsible for ensuring that activities occur as set forth in this Agreement, including ensuring that JSC meetings occur, JSC recommendations are properly reflected in the minutes, and any dispute is given prompt attention and resolved in accordance with Section 1.13.1, Section 2.1.3, Section 7.1.5 and Section 12.1, as applicable.

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

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

SCHEDULE 2.2

Alliance Management Activities

Each Alliance Manager will be the primary point of contact for the Parties regarding their collaboration under this Agreement and will be 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 [***] after the Effective Date to support the Collaboration Plans;

(c) organizing each JSC meeting, including agendas, drafting minutes, and publishing final minutes;

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

(e) preparing status and progress reports on the above as determined necessary by the JSC and ensuring that reports are produced and maintained and are of sufficient quality;

(f) assisting the JSC with completing Work Plan Reports under Section 2.7 and ensuring that such reports are provided to AstraZeneca;

(g) ensuring compliance in maintaining the Isis Internal ASO Safety Database as outlined in Section 5.4;

(h) ensuring proper approval of publications prior to submission as required in Section 11.5.5; and

(i) review material transfer agreements and keeping records of the creation and supply of materials.

SCHEDULE 2.7

WORK PLAN REPORT

[***]

SCHEDULE 2.8

AstraZeneca Bioethics Policy

The AstraZeneca Bioethics Policy is applicable to everyone involved in R&D activities including any third party who acts on our behalf.

The AstraZeneca Bioethics Policy defines the principles, behaviours and ethical standards governing our research and development worldwide. While many topics are covered by existing national laws and regulations, this policy sets out the commitment beyond ordinary legal compliance of AstraZeneca and third parties acting on AstraZeneca's behalf.

Further information on Using Animals in Research Studies at AstraZeneca is available on our web site (http://www.astrazeneca.com/Responsibility/Research-ethics/Animal-research)

AstraZeneca considers the responsible use of animals to be ethically appropriate in biomedical research and product safety testing, where suitable alternatives are not available. The following principles apply to all animal studies conducted by AstraZeneca and third parties who conduct animal studies on our behalf and to the breeding and supplying of animals for use in such studies:

- A humane approach must be adopted in the care and treatment of all animals, and the greatest consideration is given to their health and welfare, consistent with meeting the necessary scientific objectives. AstraZeneca is committed to the principles of the 3R: Replacement, Reduction and Refinement.

- All animal studies must be carefully considered and justified to ensure that the study is scientifically necessary; there is no practicable alternative to the use of animals (Replacement); only the minimum number of an appropriate species of animal will be used to achieve the scientific objectives (Reduction); and that the study is designed and undertaken to minimise pain and distress to the animals involved (Refinement).

- AstraZeneca is committed to sharing of knowledge of good practices and 3Rs achievements both throughout the AstraZeneca group of companies and the wider scientific community.

- We must ensure that our own facilities and animal welfare programmes, as well as those of third parties who conduct animal studies on our behalf, comply with our policies. All animal studies must be undertaken in compliance with all relevant local and national laws and regulations, and with the principles of the "Guide for the Care and Use of Laboratory Animals" 8th Edition, Institute for Laboratory Animal Research. Wherever possible, our preference is to work with third parties accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International (AAALAC International).

- AstraZeneca does not conduct or resource work using wild-caught non-human primates or great ape species. In the rare case where there is no credible alternative model to develop a treatment for serious disease, exceptions may be considered. The decision to progress requires rigorous secondary ethical and scientific review to challenge the need for the study, followed by AstraZeneca Board-level approval.

SCHEDULE 5.1.1

Specific Performance Milestone Events

[To be added after Collaboration Program License Right Exercise]

SCHEDULE 5.5.1

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

[***]

ЕХНІВІТ 1

AstraZeneca 5R Framework

[***]

Exhibit 10.2

AMENDMENT #6 TO RESEARCH, DEVELOPMENT AND LICENSE AGREEMENT

This **AMENDMENT #6 TO THE RESEARCH, DEVELOPMENT AND LICENSE AGREEMENT** (this "***Amendment No. 6***") is entered into and made effective as of the 2nd day of September, 2015 (the "***Amendment No. 6 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 **Glaxo Group Limited**, a company existing under the laws of England and Wales, having its registered office at 980 Great West Road, Brentford, London TW8 9GS, United Kingdom ("***GGL***"), and **Glaxosmithkline intellectual property development limited,** a company existing under the laws of England and Wales, having its registered office at 980 Great West Road, Brentford London TW8 9GS, United Kingdom ("***GSK IPDL***"). GGL and GSK IPDL are referred to together as ("***GSK***"). Isis and GSK are each referred to herein by name or as a "***Party***" or, collectively, as "***Parties***."

RECITALS

Whereas, Isis and GGL are parties to the Research, Development and License Agreement dated March 30, 2010, as amended (the "***Agreement***") and GGL has sub-licensed its intellectual property rights under the Agreement to GSK IPDL;

Whereas, Isis and GGL entered into that certain Amendment #2 to the Research, Development and License Agreement dated October 30, 2012 (the "***TTR FAP Amendment***") to amend the Agreement to more rapidly Develop the drug, ISIS-TTR_{Rx} (ISIS 420915), under the Rare Disease Program focused on the Collaboration Target, Transthyretin (the "***TTR Program***"), intended to enable ISIS-TTR_{Rx} to reach registration earlier than originally estimated; and

Whereas, Isis and GSK now desire to further amend the Agreement solely with respect to the TTR Program to, among other things, enable GSK to conduct a Phase 3 Trial of ISIS-TTR_{Rx} in patients with familial amyloid cardiomyopathy (FAC) and/or senile systemic amyloidosis (SSA) (the "***Cardiomyopathy Phase 3 Trial***"), on the terms and conditions as set forth herein.

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 TTR Program, the Parties, intending to be legally bound, do hereby agree as follows:

1. TTR Program – Cardiomyopathy Drug Development Activities.

a. **TTR Cardiomyopathy Development Plan; Cardiomyopathy Phase 3 Trial**. As of the Amendment No. 6 Date, the initial clinical study design for the Cardiomyopathy Phase 3 Trial for the TTR Program is reflected in the TTR Cardiomyopathy Development Plan and further described in the other TTR Cardiomyopathy Registration-Directed Program Documents. The TTR Cardiomyopathy Development Plan is incorporated into and made an integral part of the TTR Development Plan for the overall TTR Program. GSK will [***] conduct the Cardiomyopathy Phase 3 Trial in accordance with the TTR Cardiomyopathy Development Plan. The Parties intend the Cardiomyopathy Phase 3 Trial to meet the requirements of a Phase 3 Trial to demonstrate therapeutic benefit in patients with FAC and SSA, and for the Cardiomyopathy Phase 3 Trial and the TTR Cardiomyopathy Registration-Directed Program Documents to support registration filings and Approval of ISIS-TTR_{Rx} for FAC and/or SSA on a global basis. The Parties will mutually agree on any material changes to the TTR Cardiomyopathy Registration-Directed Program Documents in accordance with Section 7 of this Amendment No. 6.

b. **GSK's Filing of the Cardiomyopathy Phase 3 Trial IND**. GSK will be the sponsor of the Cardiomyopathy Phase 3 Trial and as such will file a separate IND (the "***Cardiomyopathy IND***") for the Cardiomyopathy Phase 3 Trial, which IND will reference Isis' existing IND for ISIS-TTR_{Rx}. Isis will have the right to review and comment on the Cardiomyopathy IND prior to GSK filing it with any Regulatory Authority and will provide any comments within [***] ([***]) business days after receipt of the Cardiomyopathy IND. GSK will discuss such proposed changes with Isis, will consider Isis' comments in good faith, [***]. Isis will execute, acknowledge and deliver such further instruments, and do all such other acts, as may be reasonably necessary in order for GSK to become the sponsor and IND-holder for the Cardiomyopathy Phase 3 Trial.

c. **Isis' Support Activities for the Cardiomyopathy Phase 3 Trial**. Isis will provide support to GSK as reasonably requested by GSK from time to time for regulatory activities for the Cardiomyopathy Phase 3 Trial, including without limitation assisting GSK with assembling the IND (which GSK will prepare and file) for the Cardiomyopathy Phase 3 Trial, and sharing information on operational aspects of the conduct of the Cardiomyopathy Phase 3 Trial and the ISIS-TTR_{Rx} Study (the "***Isis Cardiomyopathy Support Activities***"). If GSK were to request support from Isis in addition to the Isis Cardiomyopathy Support Activities, GSK will pay Isis to provide such support [***].

d. **ISIS-TTR**Rx **Safety Reporting; Regulatory Coordination**. Until [***], Isis will be and will remain the sponsor and IND-holder for ISIS-TTR_{Rx} for the Phase 2 PoC Trial for the FAP indication (the "***ISIS FAP IND***"). Isis hereby grants a right of reference to GSK to cross reference the ISIS FAP IND, and Isis will take such additional actions as reasonably requested by GSK to allow GSK to exercise its right of reference to the ISIS FAP IND. Because GSK will be the sponsor of the Cardiomyopathy Phase 3 Trial and will file the Cardiomyopathy IND for the Cardiomyopathy Phase 3 Trial, GSK and Isis agree to coordinate their respective ISIS-TTR_{Rx} Development and regulatory activities, [***], and as otherwise agreed in the applicable Safety Data Exchange Agreement. Notwithstanding the foregoing, the Parties agree that GSK will lead the regulatory interactions with the Regulatory Authorities with respect to the Cardiomyopathy Phase 3 Trial; *provided*, [***] and will consider in good faith any proposals and comments made by Isis.

e. [***], the Parties will develop and agree in writing on a drug safety information exchange agreement (the "***Safety Data Exchange Agreement***") that, with respect to the Cardiomyopathy Phase 3 Trial, will include [***] related to ISIS-TTR_{Rx}, sufficient to enable each Party to comply with its legal and regulatory obligations and internal processes and consistent with the terms of this Amendment No. 6 and the Agreement (as amended by this Amendment No. 6).

During the term of the Safety Data Exchange Agreement (which shall remain in effect until [***]), each Party will [***] report to the other Party (and provide documentation to such Party related to) any serious adverse events (SAEs), suspected unexpected serious adverse reactions (SUSARs), and any other information the other Party reasonably requires to comply with its legal and regulatory requirements as the sponsor under its respective IND for ISIS-TTR_{Rx}, in each case in accordance with the terms as set out in the Safety Data Exchange Agreement. Notwithstanding the foregoing, each Party will provide the other Party with [***] updates regarding adverse events and lab findings under any Clinical Study conducted by or on behalf of a Party for ISIS-TTR_{Rx}.

f. **Notice of Completion of Cardiomyopathy Phase 3 Trial**. GSK will deliver written notice to Isis within [***] ([***]) Business Days after the Cardiomyopathy Phase 3 Trial is Complete and, together with such notice, will provide Isis with the data generated based on the [***] (such notice and data, the "***Cardiomyopathy Phase 3 Trial Completion Package***").

g. **Decision Making**. GSK will use its Commercially Reasonable Efforts to perform its activities designated under the TTR Cardiomyopathy Development Plan giving due consideration to the recommendations and advice of the TTR Project Team. GSK will have the final decision-making authority regarding [***].

h. **Briefing the TTR Project Team.** At each regularly scheduled meeting of the TTR Project Team, GSK will provide to the TTR Project Team [***].

2. **TTR Program – Cardiomyopathy Drug Development Activities and Costs**. GSK will be responsible for all of GSK's activities under the TTR Cardiomyopathy Registration-Directed Program Documents [***], including conducting the Cardiomyopathy Phase 3 Trial. In addition, GSK will be responsible for paying [***].

3. **Manufacturing and Supply**.

a. ***API Supply for the Cardiomyopathy Phase 3 Trial***. Isis will supply to GSK up to a total of [***] API of ISIS-TTR_{RX} in accordance with the terms set forth on SCHEDULE 3. Isis and GSK are discussing [***].

b. ***Finished Drug Product Supply for the Cardiomyopathy Phase 3 Trial***. GSK will manufacture and supply, [***], Finished Drug Product for the Cardiomyopathy Phase 3 Trial, which, as of the Amendment No. 6 Date, the Parties anticipate will be manufactured by [***] at a [***].

4. **Option**. GSK may exercise its Option to the TTR Program by providing written notice to Isis of its decision to exercise its Option to the TTR Program under Section 3.1 of the Agreement on or before 5:00 p.m. (Eastern time) on the [***] ([***]) day following the [***] under scenarios (a)-(d) below:

a) GSK receives a Positive Phase 2 PoC Trial Notice from Isis; or

b) GSK receives endorsement, in accordance with [***] to prepare an NDA filing for ISIS-TTR_{Rx}; or

c) The Cardiomyopathy Phase 3 Trial is Complete; or

d) Both the Cardiomyopathy Phase 3 Trial and the Phase 2 PoC Trial are Complete or have been terminated in accordance with Section 10.a or Section 10.b of this Amendment No. 6 or under Section 11a or Section 11b of the TTR FAP Amendment or terminated under Article 9 of the Agreement;

(the "***Option Deadline***").

If GSK does not provide written notice to Isis to license the TTR Program before the Option Deadline, then GSK's Option to the TTR Program will expire and, subject to the terms of this Amendment No. 6, Section 9 of the TTR FAP Amendment and the terms of the Agreement (as amended by this Amendment No. 6), Isis will be free to [***] that were included in the TTR Program on its own or with a Third Party.

5. Following the expiration of the Option to the TTR Program, or termination of the Agreement with respect to the TTR Program, or termination of the Agreement in its entirety, GSK will have no further obligations to conduct the Cardiomyopathy Phase 3 Trial and such responsibility, following transfer of the study to Isis as set forth below, would thereafter be the sole responsibility of Isis. Promptly (but in any event within [***] ([***]) days) following the expiration or termination of GSK's Option to the TTR Program, GSK and Isis would agree upon a transfer plan and appropriate timelines for each of the activities set forth below and would initiate such activities in a diligent manner:

(a) transfer to Isis, [***], the necessary data (including manufacturing batch records and test results, and such other required manufacturing information, clinical study results and information from the Cardiomyopathy Phase 3 Trial (including transferring the Cardiomyopathy IND and sponsorship of the Cardiomyopathy Phase 3 Trial to Isis), and such [***] information in the TTR Program in the possession or control of GSK to the extent such data, results and information were generated by or on behalf of GSK under the Agreement (as amended by this Amendment No. 6);

(b) at Isis' written request, deliver to Isis any remaining stock of API in GSK's possession as of the date of such expiration or termination [***], and any remaining stock of Finished Drug Product in GSK's possession as of the date of such expiration or termination at a cost equal to [***]; provided that Isis will be responsible for [***] with respect to the transfer of the remaining stock of API and Finished Drug Product to Isis;

(c) If Isis determines in good faith that additional Finished Drug Product would be required for Isis to continue to conduct those activities planned to be conducted during the [***]-month period immediately following such expiration or termination of GSK's Option to the TTR Program, in accordance with the then-current TTR FAC Development Plan, then upon written notice from Isis to GSK, GSK will (i) supply to Isis ([***]) an amount of additional Finished Drug Product sufficient to conduct those activities actually planned for the subsequent [***]-month period under the then-current TTR Cardiomyopathy Development Plan and (ii) at Isis' request, transfer the manufacturing process used by GSK to manufacture such Finished Drug Product to [***]; and

(d) With respect to GSK's contractual relationship with Third Parties performing work for GSK for the Cardiomyopathy Phase 3 Trial (including any contract research organizations and CMOs intended for use as commercial suppliers of Finished Drug Product), at Isis' written request, GSK will [***] in establishing a relationship with such Third Party CMO and transferring activities under GSK's contractual arrangements with such Third Party CMO to Isis. GSK will also [***] to assign to Isis any stand-alone contractual manufacturing agreements (or the portion of a contractual manufacturing agreement to the extent assignable in part) that GSK may have in place with such Third Party CMO that are specific to the Cardiomyopathy Phase 3 Trial material (excluding any such agreements that cover any other GSK products or activities, or are part of a master agreement between such Third Party CMO and GSK).

6. For the avoidance of doubt, these Sections 4 and 5 expressly supersede and replace Section 5 of the TTR FAP Amendment.

7. **Material Amendments to the TTR Cardiomyopathy Registration-Directed Program Documents**.

a. ***Overview***. As of the Amendment No. 6 Date, the Parties have agreed to the TTR Cardiomyopathy Development Plan (which is attached hereto as ATTACHMENT 1) and the Cardiomyopathy Phase 3 Protocol. GSK may make non-material changes to the TTR Cardiomyopathy Development Plan, in its discretion. Any other material or non-material changes proposed to be made to the TTR Cardiomyopathy Development Plan shall be determined in accordance with Section 7 (b) or (c) below, as applicable.

b. ***Material Amendment Process***. No material amendment to any TTR Cardiomyopathy Registration-Directed Program Document (each, a "***Material Amendment***") may be made without both Parties' prior written consent. If any Regulatory Authority requires or, based on [***] or otherwise at its discretion, either Party requests a material change to the Cardiomyopathy Phase 3 Trial or any TTR Cardiomyopathy Registration-Directed Program Document that requires the Parties to make a Material Amendment to a TTR Cardiomyopathy Registration-Directed Program Document to affect such a change, the Parties will use good faith and commercially reasonable efforts to mutually agree on such a Material Amendment to such TTR Cardiomyopathy Registration-Directed Program Document within [***] ([***]) days of receiving such proposed change from such Regulatory Authority or a Party. If the Parties mutually agree to such a Material Amendment, GSK will continue to perform the Cardiomyopathy Phase 3 Trial in accordance with such amended TTR Cardiomyopathy Registration-Directed Program Documents. If, despite the Parties' good faith and commercially reasonable efforts, the Parties cannot agree (i) on such a Material Amendment to such TTR Cardiomyopathy Registration-Directed Program Document or (ii) whether such an amendment is a Material Amendment, in each case, within [***] ([***]) days of receiving such proposed change from such Regulatory Authority or at the recommendation of a Party, as applicable, the dispute will be promptly (but no later than [***] ([***]) days after the end of such [***] ([***]) day period) referred to the [***]. If the [***] cannot resolve the matter within [***] ([***]) Business Days after receiving such dispute then:

i. if the dispute arose prior to the date [***], then [***]; or

ii. if the dispute arose after the date [***], then [***].

c. ***Non-Material Amendments***. GSK will consider in good faith any changes to any TTR Cardiomyopathy Registration-Directed Program Documents that are requested by Isis that do not require the Parties to make a Material Amendment to a TTR Cardiomyopathy Registration-Directed Program Document to affect such a change.

8. **Financial Provisions**. [***], GSK will pay Isis the following amounts:

a. $[***] as a lump sum payment when [***] occurs;

b. $[***] as a lump sum payment when [***]; and

c. $[***] as a lump sum payment when [***].

For clarity, except as provided in Section 1.c, Section 10.c and SCHEDULE 3 of this Amendment No. 6, no further payments shall be owed by GSK under this Amendment No. 6. [***]. Each time a milestone event listed in items (a) through (c) above is achieved, GSK will send Isis a written notice thereof promptly (but in any event no later than [***] Business Days) following the date of achievement of such milestone event and such payment will be due within [***] days of receipt by GSK of an invoice sent from Isis.

9. **No Impact on Other Collaboration Programs**. Except as otherwise expressly amended by this Amendment No. 6, the Agreement remains in full force and effect in accordance with its terms. For the avoidance of doubt, this Amendment No. 6 is solely intended to modify certain terms of the Agreement regarding the TTR Program, and does not amend the Agreement in any way with respect to the other Collaboration Programs.

10. **Termination for a Safety Concern**.

a. ***Required by Regulatory Authorities or Mutually Agreed***. If a Safety Concern arises that causes (i) [***] or (ii) [***], then in each case [***] should be initiated within [***] ([***]) days after such request or agreement and GSK may terminate its Option to the TTR Program with [***] ([***]) days advance written notice.

b. ***Not Required by Regulatory Authorities or Mutually Agreed.*** If a Safety Concern arises that causes the Cardiomyopathy-DSMB, any Regulatory Authority, or GSK's Global Safety Board to [***], the Parties will promptly (but no later than [***] ([***]) days after such inability to agree on the [***]) meet and confer to discuss such Safety Concern and use good faith efforts to resolve such Safety Concern. If, after such good faith discussions (including discussions with the Cardiomyopathy-DSMB), [***], GSK will have the right to terminate the Cardiomyopathy Phase 3 Trial and/or the TTR Program by providing Isis written notice, which termination will become effective on the [***] ([***]) day following Isis' receipt of such termination notice.

c. ***Consequences of Termination***. If GSK terminates its Option to the TTR Program under Section 10.a or Section 10.b of this Amendment No. 6 or under Section 11a or Section 11b of the TTR FAP Amendment (i) GSK will have no obligation to make any further payments to Isis under this Amendment No. 6 (other than any payments that accrued prior to the effective date of any such termination), (ii) Isis will have no obligation to continue the Phase 2 PoC Trial or Cardiomyopathy Phase 3 Trial, (iii) GSK will pay Isis $[***] to compensate Isis for its [***] costs only if Isis directs, by written notice within [***] ([***]) days after GSK's termination notice, the clinical research organization that is engaged to conduct the Phase 2 PoC Trial to begin the process of terminating the Phase 2 PoC Trial, and (iv) GSK will pay Isis an amount equal to [***] only if, within [***] ([***]) days after GSK's termination notice, Isis delivers written notice to GSK of Isis' election to begin the process of terminating the Cardiomyopathy Phase 3 Trial.

11. **Restriction on GSK's Right to Terminate for Convenience**. Except in accordance with Section 10.a or Section 10.b of this Amendment No. 6, Section 11a or Section 11b of the TTR FAP Amendment, or Section 9.2.2, Section 9.2.3(a) or Section 9.2.5 of the Agreement, GSK will not have the right to terminate the Agreement with respect to the TTR Program (or terminate this Amendment No. 6) until the [***]

12. **Definitions**. Capitalized terms not otherwise defined herein will have the meanings given in the Agreement. For purposes of this Amendment No. 6, the following capitalized terms will have the following meanings:

a. "***API***" means bulk active pharmaceutical ingredient manufactured in accordance with cGMP (unless expressly stated otherwise) for ISIS-TTR_{Rx}.

b. "***Cardiomyopathy-DSMB***" means the Data Safety Monitoring Board for the Cardiomyopathy Phase 3 Trial.

c. "***Cardiomyopathy-DSMB Charter***" means, with respect to the Cardiomyopathy-DSMB for the Cardiomyopathy Phase 3 Trial, any charter that governs the activities and duties of such Cardiomyopathy-DSMB and specifies its members.

d. "***Cardiomyopathy IND***" has the meaning set forth in Section 1.b.

e. "***Cardiomyopathy Phase 3 Protocol***" means the protocol No. ISIS 420915-CS entitled *"A Randomised, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of GSK2998728 in Subjects with Transthyretin Amyloid Cardiomyopathy" (GSK study ID: 204650)*" for the conduct of the Cardiomyopathy Phase 3 Trial, as may be amended from time to time pursuant to Section 7 of this Amendment No. 6.

f. "***Cardiomyopathy Phase 3 Trial***" means, with respect to ISIS-TTR_{Rx}, the Phase 3, multicenter, double-blind, randomized, placebo-controlled study of ISIS-TTR_{Rx} in Cardiomyopathy patients.

g. "***Cardiomyopathy Phase 3 Trial Completion Package***" has the meaning set forth in Section 1.f.

h. "***Complete***", "***Completed***", or "***Completion***" means[***].

i. "***Dosing***" or "***Dosed***" has the meaning set forth in Section 8.

j. "***Finished Drug Product***" means any drug product containing API as an active pharmaceutical ingredient in finished bulk form.

k. "***Isis Cardiomyopathy Support Activities***" has the meaning set forth in Section 1.c.

l. "***ISIS-TTR***$_{Rx}$" means the Compound known as ISIS 420915 and also known as GSK2998728.

m. "***Material Amendment***" has the meaning set forth in Section 7.b.

n. "***Option Deadline***" has the meaning set forth in Section 4.

o. "***Positive Phase 2 PoC Trial Notice***" means, with respect to the Phase 2 PoC Trial, a written notice delivered by Isis to GSK containing (i) [***], and (ii) [***].

p. "***Safety Concern***" means [***]

q. "***Safety Data Exchange Agreement***" has the meaning set forth in Section 1.e.

r. "***TTR Cardiomyopathy Development Plan***" means the Development plan attached to this Amendment as ATTACHMENT 1, as may be amended from time to time pursuant to Section 7 of this Amendment No. 6.

s. "***TTR Cardiomyopathy Registration-Directed Program Documents***" means the TTR Cardiomyopathy Development Plan, the Cardiomyopathy Phase 3 Protocol and the Cardiomyopathy-DSMB Charter.

t. "***TTR FAP Amendment***" has the meaning set forth in the Recitals.

u. "***TTR Program***" has the meaning set forth in the Recitals.

*** - * - * - * - *[Signature page follows] * - * - * - * - ***

IN WITNESS WHEREOF, the Parties have caused this Amendment No. 6 to be executed by their duly authorized representatives as of the Amendment No. 6 Date.

ISIS PHARMACEUTICALS, INC.

By: */s/ B. Lynne Parshall*

Name: B. Lynne Parshall

Title: Chief Operating Officer

Date:

GLAXO GROUP LIMITED

By: */s/ Paul Williamson*

Name: Paul Williamson

Title: Authorised Signatory For and on behalf Of Edinburgh Pharmaceutical Industries Limited Corporate Director

Date: 9/1/15

GLAXOSMITHKLINE INTELLECTUAL PROPERTY DEVELOPMENT LIMITED

By: */s/ Paul Money*

Name: Paul Money

Title: Authorised Signatory For and on behalf Of Glaxo Group Limited Corporate Director

Date: 9/2/15

ATTACHMENT 1

[***]

SCHEDULE 3

TTR CARDIOMYOPATHY ISIS-TTR$_{RX}$ API CLINICAL SUPPLY TERMS

[***]

APPENDIX X

API Specification

[***]

EXECUTION COPY

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

Exhibit 10.3

AMENDMENT NUMBER ONE
TO THE
SECOND AMENDED AND RESTATED
STRATEGIC COLLABORATION AND LICENSE AGREEMENT

THIS AMENDMENT NUMBER ONE (the "**Amendment**") to the Second Amended and Restated Strategic Collaboration and License Agreement is entered into as of the 13 day of July, 2015 (the "**Amendment 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**"), and Isis Pharmaceuticals, Inc., a Delaware corporation, with its principal place of business at 2855 Gazelle Court, Carlsbad, California 92010 ("**Isis**").

RECITALS

WHEREAS, Isis and Alnylam granted to each other certain exclusive rights with respect to certain targets pursuant to that certain Second Amended and Restated Strategic Collaboration and License Agreement dated January 8, 2015 (the "**Second Restated Agreement**");

WHEREAS, Isis and Alnylam now desire to amend the Second Restated Agreement to expand such cross-license of exclusive rights to include additional targets as provided herein.

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 and Alnylam each agrees as follows:

1. DEFINITIONS

Capitalized terms used herein and not defined elsewhere herein have the meanings set forth in the Second Restated Agreement.

2. AMENDMENTS

2.1 Section 12 of Exhibit 1.1 of the Second Restated Agreement is deleted and replaced in its entirety by the following:

"Alnylam Exclusive Target" means an RNA Target or protein product of (a) the antithrombin gene (AT, also known as AT3), (b) the aminolevulinate synthase 1 gene (AS1), (c) the hydroxyacid oxidase 1 gene (GO1) or (d) the alpha-1 antitrypsin gene (AAT), which genes are further identified and described on Exhibit B.

2.2 Section 58 of Exhibit 1.1 of the Second Restated Agreement is deleted and replaced in its entirety by the following:

"Isis Exclusive Target" means an RNA Target or protein product of (a) the Factor XI gene (FXI), (b) the Apo(a) gene (Apoa1), (c) the diglyceride acyltransferase gene 2 (DGAT2) or (d) the growth hormone receptor gene (GHR), which genes are further identified and described on Exhibit A.

2.3 Section 100 of Exhibit 1.1 of the Second Restated Agreement is deleted and replaced in its entirety by the following:

"RNA Target" means a ribonucleic acid transcript with a defined sequence and/or function, including, for example, non-coding transcripts, pre-mRNA transcripts, and mRNA transcripts, including all splice variants and mutant forms of any such transcripts. RNA Targets may be identified by reference to a gene encoding such ribonucleic acid transcripts or, for transcripts that encode a protein, by reference to a protein encoded by such transcripts.

2.4 Exhibit A (Isis Exclusive Targets), Exhibit B (Alnylam Exclusive Targets), and Exhibit 5.3(d) (Isis Third Party Agreements) to the Second Restated Agreement are deleted and replaced with Exhibit A, Exhibit B and Exhibit 5.3(d) attached hereto, respectively. Schedules 1-8 (Alnylam Current Chemistry Patents), 1-9 (Alnylam Current Motif and Mechanism Patents), 1-14 (Alnylam Exclusive Target Patents), 1-17 (Alnylam Extended Field Patents), 1-52 (Isis Current Chemistry Patents), 1-53 (Isis Current Motif and Mechanism Patents), 1-60 (Isis Exclusive Target Patents) and 1-63 (Isis Extended Field Patents) to the Second Restated Agreement are deleted and replaced with Schedules 1-8, 1-9, 1-14, 1-17, 1-52, 1-53, 1-60 and 1-63 attached hereto, respectively.

2.5 Notwithstanding the provisions of Section 5.3(d) of the Second Restated Agreement, licenses to Isis Exclusive Target Patents that cover the manufacture, use or sale of an Alnylam Exclusive Target Product that hybridizes to and modulates the Alnylam Exclusive Target known as GO1 or the Alnylam Exclusive Target known as AAT (described in clause (c) and (d) of the definition of "Alnylam Exclusive Target", respectively) and that are subject to contractual obligations between Isis and Third Parties in effect as of the Amendment Effective Date are licensed subject to the restrictions and other terms described in the Isis Third Party Agreements. Prior to the Amendment Effective Date, Isis has provided Alnylam with copies of the Isis Third Party Agreements, provided, that Isis may redact copies of out-licenses Isis has granted Third Parties so long as the redacted terms do not limit Alnylam's rights hereunder or create obligations for Alnylam. Alnylam hereby agrees to comply, and to cause its sublicensees to comply, with such restrictions and other terms.

2.6 The license to Isis Exclusive Target Patents granted in Section 5.1(h) with respect to the Alnylam Exclusive Target known as [***]

2.7 Notwithstanding the provisions of Section 6.5(c), licenses to Alnylam Exclusive Target Patents that cover the manufacture, use or sale of an Isis Exclusive Target Product that hybridizes to and modulates an Isis Exclusive Target known as [***]

3. MISCELLANEOUS

3.1 Other Terms. All other terms and conditions of the Second Restated Agreement shall remain in full force and effect.

3.2 Representations and Warranties of the Parties. Each Party represents and warrants to the other Party that, as of the Amendment Effective Date:

(a) Such Party is duly organized and validly existing under the laws of the state of its incorporation and has full corporate power and authority to enter into this Amendment and to carry out the provisions hereof;

(b) Such Party has taken all corporate action necessary to authorize the execution and delivery of this Amendment and the performance of its obligations under this Amendment;

(c) This Amendment is a legal and valid obligation of such Party, binding upon such Party and enforceable against such Party in accordance with the terms of this Amendment. The execution, delivery and performance of this Amendment by such Party does not conflict with any agreement, instrument or understanding, oral or written, to which such Party is a Party or by which such Party may be bound, and does not violate any law or regulation of any court, governmental body or administrative or other agency having authority over such Party. All consents, approvals and authorizations from all governmental authorities or other Third Parties required to be obtained by such Party in connection with this Amendment have been obtained; and

(d) Such Party has sufficient right, power and authority to enter into this Amendment, to perform its obligations under this Amendment and to grant the licenses granted hereunder.

3.3 Counterparts. This Agreement may be executed in any number of counterparts, each of which will be deemed an 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 One to the Second Amended and Restated Strategic Collaboration and License Agreement as of the date first written above.

ALNYLAM PHARMACEUTICALS, INC.

By: */s/ John Maraganore*
Name: John Maraganore
Title: Chief Executive Officer

ISIS PHARMACEUTICALS, INC.

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

Exhibit A

Isis Exclusive Targets

1. The human Factor XI gene (also known as coagulation factor XI, plasma thromboplastin antecedent, F11, FXI). As of the Second Restatement Date, an example of an identifier for the Factor XI gene is NCBI Gene ID 2160.

2. The human Apo(a) gene (also known as apolipoprotein(a); LPA; Lipoprotein, Lp(a); Lp(a); Apo A-I; Apoa1). As of the Second Restatement Date, an example of an identifier for the Apo(a) gene is NCBI Gene ID 4018.

3. The human diacylglycerol acyltransferase 2 gene (also known as DGAT2, Acyl-CoA and diacylglycerol O-acyltransferase 2). As of the Amendment Effective Date, an example of an identifier for the DGAT2 gene is NCBI Gene ID 84649.

4. The human growth hormone receptor gene (also known as GHR, GHBP and GHIP). As of the Amendment Effective Date, an example of an identifier for the GHR gene is NCBI Gene ID 2690.

Exhibit B

Alnylam Exclusive Targets

1. The human antithrombin gene (also known asSERPINC1, antithrombin3, AT3 and ATIII). As of the Second Restatement Date, an example of an identifier for the antithrombin gene is NCBI Gene ID 462.

2. The human aminolevulinate delta-synthase gene (also known as ALAS-1, ALAS, ALAS3, ALASH, aminolevulinate delta-synthase, Delta-ALA synthase, Delta-Aminolevulinate synthase 1, 5-aminolevulinic acid synthase 1, ALAS-H, 5-aminolevulinate synthase, MIG4, aminolevulinate synthase-1, AS1). As of the Second Restatement Date, an example of an identifier for the ALAS-1 gene is NCBI Gene ID 211.

3. The human Alpha-1 antitrypsin gene (also known as AAT, SERPINA1, PI, A1A, PI1, A1AT, PRO2275, alpha1AT). As of the Amendment Effective Date, an example of an identifier for the AAT gene is NCBI Gene ID 5265.

4. The human hydroxyacid oxidase 1 gene (also known as HAO1, GO, GO1, GOX, GOX1 and HAOX1). As of the Amendment Effective Date an example of an identifier for the HAO1 gene is NCBI Gene ID 54363.

Exhibit C

[***]

EXHIBIT 5.3(D)

ISIS THIRD PARTY AGREEMENTS

The following schedule of Isis Third Party Agreements is provided by Isis to Alnylam, in connection with the Agreement. Capitalized terms used but not otherwise defined herein have the meanings given to such terms in the Agreement.

This schedule and the information and disclosures contained in this schedule are intended only to qualify and limit the licenses granted by Isis to Alnylam in the Agreement and do not expand in any way the scope or effect of any such licenses.

AGREEMENTS PROVIDING RIGHTS TO THIRD PARTIES IN CERTAIN ISIS PATENT RIGHTS

[***]

AGREEMENTS GRANTING THIRD PARTIES RIGHTS TO CONDUCT TARGET VALIDATION

[***]

RESEARCH LICENSE AGREEMENTS

[***]

AGREEMENTS CONTAINING CROSS-LICENSES TO NEW TECHNOLOGY ARISING FROM PARTNER COLLABORATIONS

[***]

GOVERNMENT RIGHTS IN ISIS IP

1. **Government Rights -** Inventions claimed in US Patent Applications: [***] were funded in part by a Small Business Innovation Research grant administered by the National Institutes of Health. Accordingly, the U.S. Federal Government retains certain rights to those inventions.

Schedule 1-8
Alnylam Current Chemistry Patents

[***]

Schedule 1-9
Alnylam Current Motif and Mechanism Patents

[***]

Schedule 1-14
Alnylam Exclusive Target Patents

[***]

Schedule 1-17
Alnylam Extended Field Patents

[***]

Schedule 1-52
Isis Current Chemistry Patents

[***]

Schedule 1-53
Isis Current Motif and Mechanism Patents

[***]

Schedule 1-60
Isis Exclusive Target Patents

[***]

Schedule 1-63
Isis Extended Field Patents

[***]

ATTACHMENT I

ISIS PHARMACEUTICALS, INC.
2011 EQUITY INCENTIVE PLAN

OPTION AGREEMENT
(NONSTATUTORY STOCK OPTION)

FOR OPTIONS GRANTED AFTER SEPTEMBER 30, 2015

Pursuant to your Stock Option Grant Notice ("***Grant Notice***") and this Option Agreement, Isis Pharmaceuticals, Inc. (the "***Company***") has granted you an option under its 2011 Equity Incentive Plan (the "***Plan***") to purchase the number of shares of the Company's Common Stock indicated in your Grant Notice at the exercise price indicated in your Grant Notice. Capitalized terms not explicitly defined in this Option Agreement but defined in the Plan shall have the same definitions as in the Plan.

The details of your option are as follows:

1. VESTING. Subject to the limitations contained herein, your option will vest as provided in your Grant Notice, provided that vesting will cease upon the termination of your Continuous Service.

2. NUMBER OF SHARES AND EXERCISE PRICE. The number of shares of Common Stock subject to your option and your exercise price per share referenced in your Grant Notice may be adjusted from time to time for Capitalization Adjustments.

3. EXERCISE RESTRICTION FOR NON-EXEMPT EMPLOYEES. In the event that you are an Employee eligible for overtime compensation under the Fair Labor Standards Act of 1938, as amended (*i.e.*, a "***Non-Exempt Employee***"), you may not exercise your option until you have completed at least six months of Continuous Service measured from the Date of Grant specified in your Grant Notice, notwithstanding any other provision of your option.

4. METHOD OF PAYMENT. Payment of the exercise price is due in full upon exercise of all or any part of your option. You may elect to make payment of the exercise price in cash or by check or in any other manner ***permitted by your Grant Notice,*** which may include one or more of the following:

(a) Provided that at the time of exercise the Common Stock is publicly traded, pursuant to a program developed under Regulation T as promulgated by the Federal Reserve Board that, prior to the issuance of Common Stock, results in either the receipt of cash (or check) by the Company or the receipt of irrevocable instructions to pay the aggregate exercise price to the Company from the sales proceeds.

(b) Subject to the consent of the Company at the time of exercise, by a "net exercise" arrangement pursuant to which the Company will reduce the number of shares of Common Stock issued upon exercise of your option by the largest whole number of shares with a Fair Market Value that does not exceed the aggregate exercise price; provided, however, that the Company shall accept a cash or other payment from you to the extent of any remaining balance of the aggregate exercise price not satisfied by such reduction in the number of whole shares to be issued; provided further, however, that shares of Common Stock will no longer be outstanding under your option and will not be exercisable thereafter to the extent that (1) shares are used to pay the exercise price pursuant to the "net exercise," (2) shares are delivered to you as a result of such exercise, and (3) shares are withheld to satisfy tax withholding obligations.

5. Minimum Number of Whole Shares. You may exercise your option only for whole shares of Common Stock. The minimum number of shares with respect to which you may exercise your option at any one time is 250, unless the number of shares available for exercise equals less than 250 shares, in which case the minimum number of shares you may exercise must equal the number of shares then available for exercise.

6. Securities Law Compliance. Notwithstanding anything to the contrary contained herein, you may not exercise your option unless the shares of Common Stock issuable upon such exercise are then registered under the Securities Act or, if such shares of Common Stock are not then so registered, the Company has determined that such exercise and issuance would be exempt from the registration requirements of the Securities Act. The exercise of your option also must comply with other applicable laws and regulations governing your option, and you may not exercise your option if the Company determines that such exercise would not be in material compliance with such laws and regulations.

7. Term. You may not exercise your option before the commencement or after the expiration of its term. The term of your option commences on the Date of Grant and expires upon the earliest of the following:

(a) three months after the termination of your Continuous Service for any reason other than upon your Disability, retirement or death; provided, however, that if during any part of such three month period your option is not exercisable solely because of the condition set forth in the section above relating to "Securities Law Compliance," your option shall not expire until the earlier of the Expiration Date or until it shall have been exercisable for an aggregate period of three months after the termination of your Continuous Service; and if (i) you are a Non-Exempt Employee, (ii) your Continuous Service terminates within six months after the Date of Grant specified in your Grant Notice, and (iii) you have vested in a portion of your option at the time of your termination of Continuous Service, your option shall not expire until the earlier of (x) the later of (A) the date that is seven months after the Date of Grant specified in your Grant Notice or (B) the date that is three months after the termination of your Continuous Service, or (y) the Expiration Date;

(b) 12 months after the termination of your Continuous Service due to your Disability;

(c) 18 months after the termination of your Continuous Service due to your retirement; provided that (i) you were over the age of 55 at the time of such retirement and (ii) you had been providing Continuous Service to the Company as an Employee, Director or Consultant (or any combination thereof) for a continuous and uninterrupted period of at least five years prior to such retirement;

(d) 18 months after your death if you die during your Continuous Service;

(e) the Expiration Date indicated in your Grant Notice; or

(f) the day before the seventh anniversary of the Date of Grant.

Notwithstanding the foregoing, if you die during the period provided in Section 7(a), 7(b) or 7(c) above, the term of your option shall not expire until the earlier of 18 months after your death, the Expiration Date indicated in your Grant Notice, or the day before the tenth anniversary of the Date of Grant.

8. EXERCISE.

(a) You may exercise the vested portion of your option (and the unvested portion of your option if your Grant Notice so permits) during its term by delivering a Notice of Exercise (in a form designated by the Company) together with the exercise price to the Secretary of the Company, or to such other person as the Company may designate, during regular business hours, together with such additional documents as the Company may then require.

(b) By exercising your option you agree that, as a condition to any exercise of your option, the Company may require you to enter into an arrangement providing for the payment by you to the Company of any tax withholding obligation of the Company arising by reason of (1) the exercise of your option, (2) the lapse of any substantial risk of forfeiture to which the shares of Common Stock are subject at the time of exercise, or (3) the disposition of shares of Common Stock acquired upon such exercise.

(c) If (i) you have not exercised your option in full by the 10th business day prior to the expiration of this option, (ii) at such time you are a current employee of the Company or were an employee of the Company within the previous 90 days, (iii) you have not otherwise instructed the broker to exercise this option prior to expiry under a separate Company-approved Rule 10b5-1 Plan, and (iv) the prevailing market price of the Common Stock exceeds the Exercise Price per share of this option, then you authorize the Company's external stock plan administrator ("Administrator") to, in its sole discretion, without obligation, and in compliance with all applicable legal conditions and restrictions, exercise this option on your behalf and sell the number of whole shares of Common Stock having a Fair Market Value sufficient to cover the aggregate exercise price plus the minimum amount of tax required to be withheld by law (such number of shares to be determined by the Company as of the date of exercise), and to remit payment of such exercise price and withholding amounts to the Company. In addition, you authorize the Company to, in its sole discretion and in compliance with all applicable legal conditions and restrictions, take any action it deems necessary or appropriate to effect such an exercise and sale.

Notwithstanding the foregoing, the Company may, in its sole discretion, without obligation, and in lieu of the automatic exercise and sale set forth above, effect a "net exercise" arrangement to cover the aggregate exercise price and minimum amount of the tax to be withheld by the Company by law, each as further described in Section 5(c)(iv) and Section 8(f) of the Plan.

You will take all necessary and appropriate actions to effect the exercise and sale under this section, including but not limited to completing any exercise forms or authorizations. You hereby authorize and appoint each of Administrator and the Company's Corporate Secretary to serve, individually or collectively, as your agent and attorney-in-fact and, in accordance with the terms of this section, to effect the exercise and sale of your option. You will pay the Company an administrative fee of $100 in connection with any exercise or sale under this section.

This Section 8(c) is intended to meet the requirements of, and comply with, Rule 10b5-1 (c) under the Exchange Act.

9. Transferability. Your option is not transferable, except (1) by will or by the laws of descent and distribution, (2) pursuant to a domestic relations order, (3) with the prior written approval of the Company, by instrument to an *inter vivos* or testamentary trust, in a form accepted by the Company, in which the option is to be passed to beneficiaries upon the death of the trustor (settlor) and (4) with the prior written approval of the Company, by gift, in a form accepted by the Company, to a permitted transferee under Rule 701 of the Securities Act.

10. Option not a Service Contract. Your option is not an employment or service contract, and nothing in your option shall be deemed to create in any way whatsoever any obligation on your part to continue in the employ of the Company or an Affiliate, or of the Company or an Affiliate to continue your employment. In addition, nothing in your option shall obligate the Company or an Affiliate, their respective stockholders, Boards of Directors, Officers or Employees to continue any relationship that you might have as a Director or Consultant for the Company or an Affiliate.

11. Withholding Obligations.

(a) At the time you exercise your option, in whole or in part, or at any time thereafter as requested by the Company, you hereby authorize withholding from payroll and any other amounts payable to you, and otherwise agree to make adequate provision for (including by means of a "cashless exercise" pursuant to a program developed under Regulation T as promulgated by the Federal Reserve Board to the extent permitted by the Company), any sums required to satisfy the federal, state, local and foreign tax withholding obligations of the Company or an Affiliate, if any, which arise in connection with your option.

(b) Upon your request and subject to approval by the Company, in its sole discretion, and compliance with any applicable legal conditions or restrictions, the Company may withhold from fully vested shares of Common Stock otherwise issuable to you upon the exercise of your option a number of whole shares of Common Stock having a Fair Market Value, determined by the Company as of the date of exercise, not in excess of the minimum amount of tax required to be withheld by law (or such lower amount as may be necessary to avoid classification of your option as a liability for financial accounting purposes). If the date of determination of any tax withholding obligation is deferred to a date later than the date of exercise of your option, share withholding pursuant to the preceding sentence shall not be permitted unless you make a proper and timely election under Section 83(b) of the Code, covering the aggregate number of shares of Common Stock acquired upon such exercise with respect to which such determination is otherwise deferred, to accelerate the determination of such tax withholding obligation to the date of exercise of your option. Notwithstanding the filing of such election, shares of Common Stock shall be withheld solely from fully vested shares of Common Stock determined as of the date of exercise of your option that are otherwise issuable to you upon such exercise. Any adverse consequences to you arising in connection with such share withholding procedure shall be your sole responsibility.

(c) You may not exercise your option unless the tax withholding obligations of the Company and/or any Affiliate are satisfied. Accordingly, you may not be able to exercise your option when desired even though your option is vested, and the Company shall have no obligation to issue a certificate for such shares of Common Stock unless such obligations are satisfied.

12. Tax Consequences. You hereby agree that the Company does not have a duty to design or administer the Plan or its other compensation programs in a manner that minimizes your tax liabilities. You shall not make any claim against the Company, or any of its Officers, Directors, Employees or Affiliates related to tax liabilities arising from your option or your other compensation. In particular, you acknowledge that this option is exempt from Section 409A of the Code only if the exercise price per share specified in the Grant Notice is at least equal to the "fair market value" per share of the Common Stock on the Date of Grant and there is no other impermissible deferral of compensation associated with the option.

13. Notices. Any notices provided for in your option or the Plan shall be given in writing and shall be deemed effectively given upon receipt or, in the case of notices delivered by mail by the Company to you, five days after deposit in the United States mail, postage prepaid, addressed to you at the last address you provided to the Company.

14. Governing Plan Document. Your option is subject to all the provisions of the Plan, the provisions of which are hereby made a part of your option, and is further subject to all interpretations, amendments, rules and regulations, which may from time to time be promulgated and adopted pursuant to the Plan. In the event of any conflict between the provisions of your option and those of the Plan, the provisions of the Plan shall control.

Exhibit 10.5

Optionee:
Date:

Isis Pharmaceuticals, Inc.
Supplemental Stock Option Agreement

Isis Pharmaceuticals, Inc. (the "Company"), pursuant to its 1989 Stock Option Plan (the "Plan") has this day granted to the undersigned optionee, an option to purchase shares of the common stock of the Company ("Common Stock") as described herein. This option is not intended to qualify and will not be treated as an "incentive stock option" within the meaning of Section 422 of the Internal Revenue Code of 1986, as amended from time to time (the "Code"). This option is subject to all of the terms and conditions as set forth herein and on Attachment I hereto, which is incorporated herein in its entirety.

Number of Shares Subject to Option:

Vesting Schedule:

Number of Shares (installment) — Date of Earliest Exercise (vesting)[1]

Exercise Price Per Share: $ [2]

Expiration Date: [3]

Percentage of Full-Time Work:

Isis Pharmaceuticals, Inc.

By: _____
Duly authorized on behalf of the Board of Directors

Optionee: _____
Address:

Optionee:
Acknowledges receipt of the option as described herein and the attachments referenced therein and understands that all rights and liabilities with respect to this option are set forth in the option and the Plan; and acknowledges that as of the date of grant of this option, it sets forth the entire understanding between the optionee and the Company regarding the acquisition of stock in the Company and supersedes all prior oral and written agreements on that subject.

[1]After the first year, the option will vest monthly with 2.08% of the total grant vesting each month; provided, however, that during any period in which the undersigned provides service at less than the Percentage of Full-Time Work set forth above, by providing written notice to you, the Company may unilaterally elect to reduce the number of shares that will vest as follows: the percentage of shares which will vest during such period of reduced service will equal (a) the percentage of shares that would vest as set forth on this schedule, multiplied by (b) the percentage of full-time work furnished during the period of reduced service divided by the Percentage of Full Time Work as set forth above. This reduction in vesting will not apply during any period of paid leave or the first 20 weeks of a period of unpaid leave. No shares will vest during unpaid leave after the first 20 weeks of such leave. Shares which do not vest because of reductions in work percentage or unpaid leave will be canceled and no longer subject to this option.

[2]Not less than 100% of the fair market value of the Common Stock on the date of grant of this option.

[3]Less than 7 years from the date of grant of this option.

ATTACHMENT I
TERMS OF **SUPPLEMENTAL** STOCK OPTION

The grant hereunder is in connection with and in furtherance of the Company's compensatory benefit plan for participation of the Company's employees (including officers), directors or consultants and is intended to comply with the provisions of Rule 701 promulgated by the Securities and Exchange Commission under the Securities Act of 1933, as amended (the "Act").

The details of your option are as follows:

1. The total number of shares of Common Stock subject to this option is set forth on the first page of the Supplemental Stock Option Agreement. Subject to the limitations contained herein, this option shall be exercisable with respect to each installment indicated in the Vesting Schedule set forth on the first page of the Supplemental Stock Option Agreement on or after the date of vesting applicable to such installment.

2. (a) The Exercise Price of this option is set forth on the first page of the Supplemental Stock Option Agreement.

(b) Payment of the exercise price per share is due in full in cash (including check) upon exercise of all or any part of each installment which has become exercisable by you.

3. The minimum number of shares with respect to which this option may be exercised at any one time is 1,000, unless the number of shares available for exercise (that is, the remaining vested shares pursuant to paragraph 1) equals less than 250 shares, in which case the minimum number of shares exercised must equal the number of shares then vested.

4. Notwithstanding anything to the contrary contained herein, this option may not be exercised unless the shares issuable upon exercise of this option are then registered under the Act or, if such shares are not then so registered, the Company has determined that such exercise and issuance would be exempt from the registration requirements of the Act.

5. The term of this option commences on the date hereof and, unless sooner terminated as set forth below or in the Plan, terminates on the Expiration Date. This option shall terminate prior to the expiration of its term as follows: 3 months after the termination of your employment with the Company or an affiliate of the Company (as defined in the Plan) for any reason or for no reason unless:

(a) such termination of employment is due to your permanent and total disability (within the meaning of Section 422(c)(6) of the Code), in which event the option shall terminate on the earlier of the termination date set forth above or 1 year following such termination of employment;

(b) such termination of employment is due to your death, in which event the option shall terminate on the earlier of the termination date set forth above or 18 months after your death; or

(c) (i) such termination of employment is due to your retirement; *and* (ii) you were over the age of 55 at the time of such retirement; *and* (iii) you had been an employee, director or consultant (or any combination thereof) of the Company for a continuous and uninterrupted period of at least 5 years prior to such retirement, in which event (*i.e* having satisfied all of the conditions set forth in clauses (i) through (iii) above) the option shall terminate on the earlier of the termination date set forth above or 18 months after such retirement; or

(d) during any part of such 3 month period the option is not exercisable solely because of the condition set forth in paragraph 4 above, in which event the option shall not terminate until the earlier of the termination date set forth above or until it shall have been exercisable for an aggregate period of 3 months after the termination of employment; or

(e) exercise of the option within 3 months after termination of your employment with the Company or with an affiliate would result in liability under Section 16(b) of the Securities Exchange Act of 1934, in which case the option will terminate on the earlier of the termination date set forth above, the 10th day after the last date upon which exercise would result in such liability or 6 months and 10 days after the termination of your employment with the Company or an affiliate.

However, this option may be exercised following termination of employment only as to that number of shares as to which it was exercisable on the date of termination of employment under the provision of paragraph 1 of this option.

6. (a) This option may be exercised, to the extent specified above, by delivering a notice of exercise (in a form designated by the Company) together with the exercise price to the Secretary of the Company, or to such other person as the Company may designate, during regular business hours, together with such additional documents as the Company may then require pursuant to subparagraph 5(f) of the Plan.

(b) By exercising this option you agree that:

(i) the Company may require you to enter an arrangement providing for the cash payment by you to the Company of any tax withholding obligation of the Company arising by reason of: the exercise of this option; the lapse of any substantial risk of forfeiture to which the shares are subject at the time of exercise; or the disposition of shares acquired upon such exercise.

(c) If (i) you have not exercised your option in full by the 10th business day prior to the expiration of this option, (ii) at such time you are a current employee of the Company or were an employee of the Company within the previous 90 days, (iii) you have not otherwise instructed the broker to exercise this option prior to expiry under a separate Company-approved Rule 10b5-1 Plan, and (iv) the prevailing market price of the Common Stock exceeds the Exercise Price per share of this option, then you authorize the Company's external stock plan administrator ("Administrator") to, in its sole discretion, without obligation, and in compliance with all applicable legal conditions and restrictions, exercise this option on your behalf and sell the number of whole shares of Common Stock having a fair market value sufficient to cover the aggregate exercise price plus the minimum amount of tax required to be withheld by law (such number of shares to be determined by the Company as of the date of exercise), and to remit payment of such exercise price and withholding amounts to the Company. In addition, you authorize the Company to, in its sole discretion and in compliance with all applicable legal conditions and restrictions, take any action it deems necessary or appropriate to effect such an exercise and sale.

You will take all necessary and appropriate actions to effect the exercise and sale under this section, including but not limited to completing any exercise forms or authorizations. You hereby authorize and appoint each of Administrator and the Company's Corporate Secretary to serve, individually or collectively, as your agent and attorney-in-fact and, in accordance with the terms of this section, to effect the exercise and sale of your option.

You will pay the Company an administrative fee of $100 in connection with any exercise or sale under this section.

This Section 6(c) is intended to meet the requirements of, and comply with, Rule 10b5-1 (c) under the Exchange Act.

7. This option is not transferable except by will or by the laws of descent and distribution, and is exercisable during your lifetime only by you; notwithstanding the foregoing, you may transfer part or all of this option to any of the following:

(i) your spouse, children (by birth or adoption), stepchildren, grandchildren, or parents;

(ii) a trust or other entity established solely for your benefit or the benefit of your spouse, children (by birth or adoption), stepchildren, grandchildren, or parents for estate planning purposes; or,

(iii) an organization which is exempt from taxation under Section 501(c)(3) of the Code or to which tax-deductible charitable contributions may be made under Section 170 of the Code.

Furthermore, you may, by delivering written notice to the Company, in a form satisfactory to the Company, designate a third party who, in the event of your death, will thereafter be entitled to exercise the option.

8. This option is not an employment contract and nothing in this option shall be deemed to create in any way whatsoever any obligation on your part to continue in the employ of the Company, or of the Company to continue your employment with the Company. In the event that this option is granted to you in connection with the performance of services as a consultant or director, references to employment, employee and similar terms shall be deemed to include the performance of services as a consultant or a director, as the case may be, provided, however, that no rights as an employee shall arise by reason of the use of such terms.

9. Any notices provided for in this option or the Plan shall be given in writing and shall be deemed effectively given upon receipt or, in the case of notices delivered by the Company to you, 5 days after deposit in the United States mail, postage prepaid, addressed to you at the address specified on the attached or at such other address as you hereafter designate by written notice to the Company.

10. This option is subject to all the provisions of the Plan, a copy of which is attached hereto and its provisions are hereby made a part of this option, including without limitation the provisions of paragraph 5 of the Plan relating to option provisions, and is further subject to all interpretations, amendments, rules and regulations which may from time to time be promulgated and adopted pursuant to the Plan. In the event of any conflict between the provisions of this option and those of the Plan, the provisions of the Plan shall control.

Attachments:

1989 Stock Option Plan
Notice of Exercise

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 9, 2015

/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 9,2015

/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, 2015, 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 9, 2015

/s/ Stanley T. Crooke	/s/ Elizabeth L. Hougen
Stanley T. Crooke, M.D., Ph.D. Chief Executive Officer	Elizabeth L. Hougen 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.