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 June 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 July 30, 2015 was 119,962,306.

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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)

	June 30, 2015 (Unaudited)	December 31, 2014
ASSETS		
Current assets:		
Cash and cash equivalents	$ 119,487	$ 142,998
Short-term investments	635,447	585,834
Contracts receivable	3,264	3,903
Inventories	6,782	6,290
Investment in Regulus Therapeutics Inc.	60,604	81,881
Other current assets	29,868	15,691
Total current assets	855,452	836,597
Property, plant and equipment, net	89,692	88,958
Licenses, net	1,753	2,690
Patents, net	19,060	17,186
Deposits and other assets	10,301	10,378
Total assets	$ 976,258	$ 955,809
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 10,954	$ 17,984
Accrued compensation	7,915	12,302
Accrued liabilities	23,753	30,451
Current portion of long-term obligations	1,225	2,882
Current portion of deferred contract revenue	58,285	51,713
Total current liabilities	102,132	115,332
Long-term deferred contract revenue	108,128	127,797
1 percent convertible senior notes	337,158	327,486
2¾ percent convertible senior notes	49,160	48,014
Long-term obligations, less current portion	7,392	7,669
Long-term financing liability for leased facility	71,968	71,731
Total liabilities	675,938	698,029
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 119,881,615 and 118,442,726 shares issued and outstanding at June 30, 2015 and December 31, 2014, respectively	120	118
Additional paid-in capital	1,269,452	1,224,509
Accumulated other comprehensive income	18,411	39,747
Accumulated deficit	(987,663)	(1,006,594)
Total stockholders' equity	300,320	257,780
Total liabilities and stockholders' equity	$ 976,258	$ 955,809

See accompanying notes.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2015	2014	2015	2014
Revenue:				
Research and development revenue under collaborative agreements	$ 119,658	$ 56,628	$ 181,551	$ 76,177
Licensing and royalty revenue	770	448	1,461	9,060
Total revenue	120,428	57,076	183,012	85,237
Expenses:				
Research, development and patent expenses	68,007	59,264	132,454	112,712
General and administrative	7,775	4,462	15,241	8,842
Total operating expenses	75,782	63,726	147,695	121,554
Income (loss) from operations	44,646	(6,650)	35,317	(36,317)
Other income (expense):				
Investment income	917	671	1,761	1,328
Interest expense	(9,127)	(4,961)	(18,148)	(9,904)
Gain (loss) on investments, net	1	(260)	1	137
Income (loss) before income tax (expense) benefit	36,437	(11,200)	18,931	(44,756)
Income tax (expense) benefit	(789)	(881)	—	1,395
Net income (loss)	$ 35,648	$ (12,081)	$ 18,931	$ (43,361)
Basic net income (loss) per share	$ 0.30	$ (0.10)	$ 0.16	$ (0.37)
Diluted net income (loss) per share	$ 0.29	$ (0.10)	$ 0.15	$ (0.37)
Shares used in computing basic net income (loss) per share	119,742	117,588	119,348	117,359
Shares used in computing diluted net income (loss) per share	127,779	117,588	124,061	117,359

See accompanying notes.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2015	2014	2015	2014
Net income (loss)	$ 35,648	$ (12,081)	$ 18,931	$ (43,361)
Unrealized (losses) gains on securities, net of tax	(28,703)	(4,456)	(21,336)	3,806
Reclassification adjustment for realized losses (gains) included in net income (loss)	—	175	—	(167)
Comprehensive income (loss)	$ 6,945	$ (16,362)	$ (2,405)	$ (39,722)

See accompanying notes.

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

	Six Months Ended June 30,	
	2015	**2014**
Operating activities:		
Net income (loss)	$ 18,931	$ (43,361)
Adjustments to reconcile net income (loss) to net cash provided by (used in) operating activities:		
Depreciation	3,406	3,141
Amortization of patents	648	543
Amortization of licenses	937	941
Amortization of premium on investments, net	3,377	3,847
Amortization of debt issuance costs	555	272
Amortization of 2¾ percent convertible senior notes discount	1,146	3,366
Amortization of 1 percent convertible senior notes discount	9,672	—
Amortization of long-term financing liability for leased facility	3,327	3,306
Stock-based compensation expense	26,910	14,777
Gain on investments, net	(1)	(137)
Non-cash losses related to patents, licensing and property, plant and equipment	166	325
Tax benefit from other unrealized gains on securities	—	(1,395)
Changes in operating assets and liabilities:		
Contracts receivable	639	(30,839)
Inventories	(492)	257
Other current and long-term assets	(14,628)	(695)
Accounts payable	(8,197)	1,991
Accrued compensation	(4,387)	(5,738)
Deferred rent	167	69
Accrued liabilities	(6,698)	1,965
Deferred contract revenue	(13,097)	(18,978)
Net cash provided by (used in) operating activities	22,381	(66,343)
Investing activities:		
Purchases of short-term investments	(240,570)	(179,196)
Proceeds from the sale of short-term investments	187,522	175,777
Purchases of property, plant and equipment	(3,940)	(3,100)
Acquisition of licenses and other assets, net	(1,749)	(1,791)
Proceeds from the sale of strategic investments	—	737
Net cash used in investing activities	(58,737)	(7,573)
Financing activities:		
Proceeds from equity awards	18,035	13,416
Principal payments on debt and capital lease obligations	(5,190)	(5,392)
Net cash provided by financing activities	12,845	8,024
Net decrease in cash and cash equivalents	(23,511)	(65,892)
Cash and cash equivalents at beginning of period	142,998	159,973
Cash and cash equivalents at end of period	$ 119,487	$ 94,081
Supplemental disclosures of cash flow information:		
Interest paid	$ 3,377	$ 2,920
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 1,166	$ 453

See accompanying notes.

1. Basis of Presentation

The unaudited interim condensed consolidated financial statements for the three and six months ended June 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, either individually or in combination, 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

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. We recognize revenue as we deliver each item under the arrangement. For example, we recognized revenue for the exclusive license we granted Bayer for ISIS-FXI$_{Rx}$ in the second quarter of 2015 because that is 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 ISIS-SMN$_{Rx}$ for spinal muscular atrophy, or SMA. As part of the collaboration, we received a $29 million upfront payment and we are responsible for global development of ISIS-SMN$_{Rx}$ through completion of Phase 2/3 clinical trials.

- In June 2012, we entered into a second and separate collaboration agreement with Biogen 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 June 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. 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 six months ended June 30, 2015 and 2014. Total inventory, which consisted of raw materials, was $6.8 million and $6.3 million as of June 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 income (loss) per share

We compute basic net income (loss) per share by dividing the net income or loss by the weighted-average number of common shares outstanding during the period. Common stock from the following items impact our common equivalent shares:

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

For the three and six months ended June 30, 2015, we had net income. As a result, we computed diluted net income per share using the weighted-average number of common shares and dilutive common equivalent shares outstanding during those periods. Diluted common equivalent shares for the three and six months ended June 30, 2015 consisted of the following (in thousands):

Three Months Ended June 30, 2015	**Income (Numerator)**	**Shares (Denominator)**	**Per-Share Amount**
Income available to common shareholders	$ 35,648	119,742	$ 0.30
Effect of diluted securities:			
Shares issuable upon exercise of stock options		3,974	
Shares issuable upon restricted stock award issuance		376	
Shares issuable related to our ESPP		4	
Shares issuable related to our 2¾ percent notes	1,047	3,683	
Income available to common shareholders, plus assumed conversions	$ 36,695	127,779	$ 0.29

Six Months Ended June 30, 2015	**Income (Numerator)**	**Shares (Denominator)**	**Per-Share Amount**
Income available to common shareholders	$ 18,931	119,348	$ 0.16
Effect of diluted securities:			
Shares issuable upon exercise of stock options		4,310	
Shares issuable upon restricted stock award issuance		399	
Shares issuable related to our ESPP		4	
Shares issuable related to our 2¾ percent notes	—	—	
Income available to common shareholders, plus assumed conversions	$ 18,931	124,061	$ 0.15

For the three and six months ended June 30, 2015, the calculation excludes the 1 percent notes because the effect on diluted earnings per share would be anti-dilutive. For the six months ended June 30, 2015, the calculation excludes the 2¾ percent notes because the effect on diluted earnings per share would be anti-dilutive. For the three and six months ended June 30, 2014 we incurred a net loss, therefore 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.

Consolidation of variable interest entities

We identify entities as variable interest entities either: (1) that do not have sufficient equity investment at risk to permit the entity to finance its activities without additional subordinated financial support, or (2) in which the equity investors lack an essential characteristic of a controlling financial interest. We perform ongoing qualitative assessments of our variable interest entities to determine whether we have a controlling financial interest in the variable interest entity and therefore are the primary beneficiary. As of June 30, 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 June 30, 2015, the total carrying value of our investments in variable interest entities was $60.6 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 income

Accumulated other comprehensive 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 income to our condensed consolidated statement of operations. The following table summarizes changes in accumulated other comprehensive income for the three and six months ended June 30, 2015 and 2014 (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2015	2014	2015	2014
Beginning balance accumulated other comprehensive income	$ 47,114	$ 29,000	$ 39,747	$ 21,080
Unrealized (losses) gains on securities, net of tax (1)	(28,703)	(4,456)	(21,336)	3,806
Amounts reclassified from accumulated other comprehensive income (2)	—	175	—	(167)
Net current period other comprehensive (loss) income	(28,703)	(4,281)	(21,336)	3,639
Ending balance accumulated other comprehensive income	$ 18,411	$ 24,719	$ 18,411	$ 24,719

(1) Other comprehensive loss for the three months ended June 30, 2015 includes income tax benefit of $5.1 million, compared to $2.9 million for the same period in 2014. For the six months ended June 30, 2014 other comprehensive income includes income tax expense of $2.5 million. There was no tax expense or benefit for the six months ended June 30, 2015.

(2) 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 six months ended June 30, 2015 and 2014, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Six Months Ended June 30,	
	2015	**2014**
Risk-free interest rate	1.5%	1.6%
Dividend yield	0.0%	0.0%
Volatility	53.6%	50.6%
Expected life	4.5 years	4.6 years

ESPP:

	Six Months Ended June 30,	
	2015	**2014**
Risk-free interest rate	0.1%	0.1%
Dividend yield	0.0%	0.0%
Volatility	56.2%	59.0%
Expected life	6 months	6 months

We did not grant any stock options or RSUs to the Board of Directors for the six months ended June 30, 2015.

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 for the six months ended June 30, 2015 was $68.73 per share.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2015	**2014**	**2015**	**2014**
Research, development and patent expenses	$ 10,465	$ 6,401	$ 20,951	$ 12,274
General and administrative	3,140	1,307	5,959	2,503
Total	$ 13,605	$ 7,708	$ 26,910	$ 14,777

Non-cash stock-based compensation expense was $13.6 million and $26.9 million for the three and six months ended June 30, 2015, respectively, and increased compared to $7.7 million and $14.8 million for the same periods in 2014 primarily due to the increase in our stock price during the first quarter of 2015 compared to the same period in 2014. As of June 30, 2015, total unrecognized estimated non-cash stock-based compensation expense related to non-vested stock options and RSUs was $57.5 million and $21.3 million, respectively. We will adjust total unrecognized compensation cost for future changes in estimated forfeitures. We expect to recognize the cost of non-cash, stock-based compensation expense related to non-vested stock options and RSUs over a weighted average amortization period of 1.4 years and 1.6 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 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 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 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 can choose to adopt it either prospectively or retrospectively. We will adopt this guidance in our fiscal year beginning January 1, 2016. We are currently evaluating the impact, if any, of the adoption of this newly issued guidance to our condensed consolidated financial statements.

3. Investments

As of June 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 June 30, 2015:

One year or less	54%
After one year but within two years	29%
After two years but within three and a half years	17%
Total	100%

As illustrated above, at June 30, 2015, 83 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 June 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.

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

June 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	$ 189,487	$ 37	$ (90)	$ —	$ 189,434
Debt securities issued by U.S. government agencies	81,639	5	(11)	—	81,633
Debt securities issued by states of the United States and political subdivisions of the states (2)	59,835	22	(58)	—	59,799
Total securities with a maturity of one year or less	330,961	64	(159)	—	330,866
Corporate debt securities	234,088	52	(848)	—	233,292
Debt securities issued by U.S. government agencies	28,002	10	(3)	—	28,009
Debt securities issued by states of the United States and political subdivisions of the states	62,203	32	(189)	—	62,046
Total securities with a maturity of more than one year	324,293	94	(1,040)	—	323,347
Total available-for-sale securities	$ 655,254	$ 158	$ (1,199)	$ —	$ 654,213
Equity securities:					
Regulus Therapeutics Inc.	$ 12,477	$ 48,127	$ —	$ —	$ 60,604
Securities included in other current assets	880	—	—	(880)	—
Total equity securities	$ 13,357	$ 48,127	$ —	$ (880)	$ 60,604
Total available-for-sale and equity securities	$ 668,611	$ 48,285	$ (1,199)	$ (880)	$ 714,817

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 June 30, 2015 were as follows (in thousands):

	Number of Investments	Less than 12 months of temporary impairment: Estimated Fair Value	Less than 12 months of temporary impairment: Unrealized Losses	More than 12 months of temporary impairment: Estimated Fair Value	More than 12 months of temporary impairment: Unrealized Losses	Total temporary impairment: Estimated Fair Value	Total temporary impairment: Unrealized Losses
Corporate debt securities	254	$ 296,493	$ (894)	$ 9,263	$ (44)	$ 305,756	$ (938)
Debt securities issued by U.S. government agencies	12	62,116	(14)	—	—	62,116	(14)
Debt securities issued by states of the United States and political subdivisions of the states	49	51,616	(178)	6,229	(69)	57,845	(247)
Total temporarily impaired securities	315	$ 410,225	$ (1,086)	$ 15,492	$ (113)	$ 425,717	$ (1,199)

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 six months ended June 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 June 30, 2015 and December 31, 2014 (in thousands):

	At June 30, 2015	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 89,072	$ 89,072	$ —	$ —
Corporate debt securities (2)	422,726	—	422,726	—
Debt securities issued by U.S. government agencies (2)	109,642	—	109,642	—
Debt securities issued by states of the United States and political subdivisions of the states (3)	121,845	—	121,845	—
Investment in Regulus Therapeutics Inc.	60,604	60,604	—	—
Total	$ 803,889	$ 149,676	$ 654,213	$ —

	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) $18.8 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.

(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 six months ended June 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 June 30, 2015)	$ —

Other Fair Value Disclosures

Our 1 percent and 2¾ percent notes had a fair value of $538.4 million and $229.9 million, respectively at June 30, 2015. We determine the fair value of our notes based on quoted market prices for these notes, which are Level 2 measurements.

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 June 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 June 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 June 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 June 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 entered into a separate collaboration agreement to discover and develop antisense therapies for cardiovascular, metabolic and renal diseases. We and AstraZeneca will also conduct research to optimize the use of our antisense technology in the kidney and other tissues. AstraZeneca has the option to license a drug for each target advanced under this research collaboration. If AstraZeneca exercises its option, it will be responsible for all further global development, regulatory and commercialization activities for such drug. Under the terms of the agreement, we will receive a $65 million upfront payment, which we expect to amortize through July 2021 beginning in the third quarter of 2015. 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 up to $25 million if we and AstraZeneca advance our first drug 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 agreement. This transaction is subject to clearance under the Hart-Scott-Rodino Antitrust Improvement Act.

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 six months ended June 30, 2015, we earned revenue of $0.7 million and $1.5 million, respectively, from our relationship with AstraZeneca. In comparison, we earned $15.6 million and $19.1 million for the same periods in 2014. Our condensed consolidated balance sheet at June 30, 2015 included deferred revenue of $3.2 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}$ over the period of our performance.

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 $55 million upon the advancement of the program following a Phase 2 study of ISIS-FXI$_{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 six months ended June 30, 2015, we earned revenue of $91.5 million from our relationship with Bayer, which represented 76 percent and 50 percent, respectively, of our total revenue for those periods. Our condensed consolidated balance sheet at June 30, 2015 included deferred revenue of $8.5 million related to our relationship with Bayer.

Biogen

We have established four strategic collaborations with Biogen that broaden and expand our severe and rare disease franchise for neurological disorders.

ISIS-SMN$_{Rx}$

In January 2012, we entered into a collaboration agreement with Biogen to develop and commercialize ISIS-SMN$_{Rx}$ for the treatment of SMA. We are currently conducting a Phase 3 study evaluating ISIS-SMN$_{Rx}$ in infants with SMA and a Phase 3 study evaluating ISIS-SMN$_{Rx}$ in children with SMA. In addition, we are evaluating ISIS-SMN$_{Rx}$ 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 ISIS-SMN$_{Rx}$ 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 ISIS-SMN$_{Rx}$. 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 ISIS-SMN$_{Rx}$ to include conducting the open-label extension study for the Phase 3 studies in infants and children, which we expect to start later this year. As a result of the change to the development plan, we are eligible to earn additional milestone and other payments.

We received an upfront payment of $29 million, which we are amortizing through February 2017. We are also eligible to receive a license fee, milestone payments and tiered royalties up to the mid-teens on any product sales of ISIS-SMN$_{Rx}$. 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 $121 million in substantive milestone and other payments associated with the clinical development of ISIS-SMN$_{Rx}$ prior to licensing and up to $150 million in substantive milestone payments if Biogen achieves pre-specified regulatory milestones. In the first half of 2015, we earned a $9 million milestone payment for advancing the Phase 3 study of ISIS-SMN$_{Rx}$ in infants with SMA and we earned a $7 million milestone payment for advancing the open-label extension study of ISIS-SMN$_{Rx}$ in children with SMA. From inception through June 2015, we have received nearly $110 million in payments for advancing ISIS-SMN$_{Rx}$, not including $10.7 million in milestone payments we earned in July 2015 for further advancing the Phase 3 study in infants and advancing the Phase 2 study in children. We will earn the next milestone payment of $11 million upon initiation of the open-label extension study of ISIS-SMN$_{Rx}$ for the Phase 3 studies in infants and 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 myotonic dystrophy type 1, or 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 $12 million, which we are amortizing through June 2017. In June 2015, we and Biogen amended the development plan for ISIS-DMPK-2.5$_{Rx}$, for which we are eligible to earn additional milestone payments of up to $4.2 million for further advancing the Phase 1 study of ISIS-DMPK-2.5$_{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 June 2015, we have received $36 million in payments for advancing ISIS-DMPK-2.5$_{Rx}$. We will earn the next milestone payment of $2.8 million if we further advance the Phase 1 study for ISIS-DMPK-2.5$_{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 June 2015, we have received $40 million in payments under this collaboration. We will earn the next milestone payment of $10 million if we initiate an IND-enabling toxicology study for a drug 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 June 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 six months ended June 30, 2015, we earned revenue of $17.8 million and $57.0 million, respectively, from our relationship with Biogen, which represented 15 percent and 31 percent, respectively, of our total revenue for those periods. In comparison, we earned revenue of $34.5 million and $44.7 million for the same periods in 2014. Our condensed consolidated balance sheet at June 30, 2015 included deferred revenue of $105.0 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 a $35 million upfront payment and in May 2011 we received a $3 million payment when we and GSK expanded the collaboration.

In October 2012, we and GSK amended the original agreement to reflect an accelerated clinical development plan for ISIS-TTR_{Rx}. From inception through June 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 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 $220.5 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 June 2015, we have received $129.5 million in payments under this strategic alliance with GSK. We will earn the next milestone payment of $5 million if we further advance ISIS-$GSK4_{Rx}$. 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 six months ended June 30, 2015, we earned revenue of $4.3 million and $20.8 million, respectively, from our relationship with GSK, which represented four percent and 11 percent, respectively, of our total revenue for those periods. In comparison, we earned revenue of $3.5 million and $6.8 million for the same periods in 2014. Our condensed consolidated balance sheet at June 30, 2015 included deferred revenue of $6.2 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 April 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 June 2015, we have received $30 million in payments under this strategic alliance with Roche, not including the $22 million milestone payment we earned in July 2015 when we initiated a Phase 1 trial for 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 six months ended June 30, 2015, we earned revenue of $2.4 million and $4.8 million, respectively, from our relationship with Roche. In comparison, we earned $2.4 million and $4.4 million for the same periods in 2014. Our condensed consolidated balance sheet at June 30, 2015 included deferred revenue of $12.9 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 income (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 six months ended June 30, 2015 (in thousands).

Three Months Ended June 30, 2015	Isis Core	Akcea Therapeutics	Total
Revenue:			
Research and development	$ 119,658	$ —	$ 119,658
Licensing and royalty	770	—	770
Total segment revenue	$ 120,428	$ —	$ 120,428
Income (loss) from operations	$ 53,588	$ (8,942)	$ 44,646

Six Months Ended June 30, 2015	Isis Core	Akcea Therapeutics	Total
Revenue:			
Research and development	$ 181,551	$ —	$ 181,551
Licensing and royalty	1,461	—	1,461
Total segment revenue	$ 183,012	$ —	$ 183,012
Income (loss) from operations	$ 51,357	$ (16,040)	$ 35,317

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

Three Months Ended June 30, 2014	Isis Core	Akcea Therapeutics	Total
Revenue:			
Research and development	$ 56,628	$ —	$ 56,628
Licensing and royalty	448	—	448
Total segment revenue	$ 57,076	$ —	$ 57,076
Loss from operations	$ (1,042)	$ (5,608)	$ (6,650)

Six Months Ended June 30, 2014	Isis Core	Akcea Therapeutics	Total
Revenue:			
Research and development	$ 76,177	$ —	$ 76,177
Licensing and royalty	9,060	—	9,060
Total segment revenue	$ 85,237	$ —	$ 85,237
Loss from operations	$ (26,653)	$ (9,664)	$ (36,317)

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2015	2014	2015	2014
Partner A	76 %	0 %	50 %	0 %
Partner B	15 %	60 %	31 %	52 %
Partner C	4 %	6 %	11 %	8 %
Partner D	1 %	27 %	1 %	22 %

Contracts receivable from three significant partners comprised approximately 100 percent and 99 percent of our contract receivables at June 30, 2015 and December 31, 2014, respectively.

8. Subsequent Event

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 will recognize in the third quarter of 2015. We remain a significant shareholder of Regulus' common stock.

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 therapeutic and commercial potential of our technologies and drugs, including KYNAMRO, volanesorsen (formerly ISIS-APOCIII$_{Rx}$), ISIS-SMN$_{Rx}$ 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 32 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$_{Rx}$, ISIS-SMN$_{Rx}$ 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 severe, rare, genetic and often fatal, disease in which patients experience progressive buildup of amyloid plaque deposits in tissues throughout the body, including peripheral nerves and cardiac muscle. ISIS-SMN$_{Rx}$ 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 several 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, including Mexico, Argentina, South Korea, Ecuador and Peru, 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’s development plan combines short-term indications, which have the potential for early market entrance in patients with limited therapeutic options, with long-term indications in 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 GI 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 ISIS-SMN$_{Rx}$, which is in Phase 3 development. We currently have four drugs we are advancing through these collaborations, ISIS-SMN$_{Rx}$, ISIS-DMPK$_{Rx}$, ISIS-BIIB3$_{Rx}$ and ISIS BIIB4$_{Rx}$. 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 therapies 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. Akcea is focused on the development and commercialization of volanesorsen, ISIS-APO(a)$_{Rx}$ and ISIS-ANGPTL3$_{Rx}$, as well as more potent follow on drugs for these programs. 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 the most advanced of its drugs, volanesorsen. 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 exploit 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 sold a portion of our Regulus stock for more than $45 million of cash, 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 $1.5 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 design and execute our patent strategy to provide us with extensive protection for our drugs and our technology. With our ongoing research and development, we continue to add to our substantial patent estate. Our patents not only protect our key assets—our technology and our drugs—they also form the basis for lucrative licensing and partnering arrangements. Through June 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

Corporate Highlights *(2015 second quarter and subsequent activities)*

- We licensed ISIS-FXI$_{Rx}$ to Bayer to develop and commercialize ISIS-FXI$_{Rx}$ for the prevention of thrombosis.
  - We generated a $100 million upfront payment from Bayer and are eligible to earn up to $275 million in additional payments, including a $55 million milestone payment upon advancement of the program following completion of the planned Phase 2 study.
  - We are eligible to receive tiered royalties in the low to high 20 percent range on gross margins of ISIS-FXI$_{Rx}$.
- We and AstraZeneca formed a multi-year collaboration to discover and develop novel antisense drugs primarily focused on treating cardiovascular, metabolic and kidney diseases.
  - In total, we have the potential to earn up to more than $4 billion in license fees and milestone payments.
    - We will receive a $65 million upfront payment from AstraZeneca and we are eligible to earn substantial development and regulatory milestone payments and license fees. We are eligible to earn a payment of $25-30 million under this collaboration next year 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.
    - This transaction is subject to clearance under the Hart-Scott-Rodino Antitrust Improvements Act.
- To date this year, we have generated nearly $300 million in payments from our partners.

Drug Development Highlights (*2015 second quarter and subsequent activities*)

- We reported positive clinical results from KYNAMRO, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$. These data exemplify the broad applicability and potential for antisense drugs to provide therapeutic benefit for many different diseases.
  - We reported that the FOCUS FH study evaluating KYNAMRO in patients with severe heterozygous familial hypercholesterolemia met its primary 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 presented positive results based on an April 17, 2015 data analysis from the ongoing open-label Phase 2 clinical study of ISIS-SMN$_{Rx}$ in infants with Type I spinal muscular atrophy. The data reported showed continued increases in median event-free survival and muscle function scores as well as achievement of developmental milestones.
  - We provided an update based on a May 15, 2015 data analysis in children with spinal muscular atrophy who have completed the open-label, Phase 2 multiple-dose study of ISIS-SMN$_{Rx}$ and are continuing to receive treatment in an open-label extension study. Consistent with earlier observations, increases in muscle function scores and additional motor function tests were observed in children treated with ISIS-SMN$_{Rx}$.
  - Dr. Merrill Benson, an investigator of ISIS-TTR$_{Rx}$, reported positive data from an investigator-initiated study in patients with TTR amyloid-related cardiomyopathy. In this study, Dr. Benson observed apparent stabilization of cardiac disease after six months of treatment with ISIS-TTR$_{Rx}$ with no progression of cardiac disease. Patients also experienced up to 88 percent reduction in TTR after nine months of dosing compared to baseline.
  - We reported positive results from an ongoing open-label extension study of ISIS-TTR$_{Rx}$ in patients with familial amyloid polyneuropathy, or FAP. In the open-label study after thirteen weeks of treatment with ISIS-TTR$_{Rx}$, TTR protein was reduced up to 92 percent with a median reduction of 78 percent in patients with FAP compared to their baseline TTR levels at entry into the Phase 3 study.
  - We reported positive Phase 2 data for ISIS-GCCR$_{Rx}$ in patients with type 2 diabetes. In this study after six weeks of treatment with ISIS-GCCR$_{Rx}$, patients achieved improvements in multiple measures of glucose control with trends toward improvements in insulin sensitivity.

- We published clinical data from our novel lipid drugs, volanesorsen and ISIS-APO(a)$_{Rx}$, in the New England Journal of Medicine and The Lancet, respectively, two prestigious medical journals. These data highlight the significant interest from the medical community in our lipid drugs and the significance of the clinical data from these programs.
- Volanesorsen was granted orphan drug designation from the US FDA for the treatment of patients with FCS.
- We continued to advance our pipeline of drugs.
  - We initiated a Phase 1/2 study of ISIS-HTT$_{Rx}$ in patients with Huntington's disease (HD). ISIS-HTT$_{Rx}$ has been 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 patients who are obese.

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

- Assessing the propriety of revenue recognition and associated deferred revenue;
- Determining the proper valuation of investments in marketable securities and other equity investments;
- 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 six months ended June 30, 2015 was $120.4 million and $183.0 million, respectively, compared to $57.1 million and $85.2 million for the same periods in 2014. We recognized $91.2 million in connection with our recently completed exclusive license agreement with Bayer in the second quarter of 2015. We also earned $56.8 million in revenue from milestone payments from our partners in the first half of 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. Excluding the revenue from Bayer, we expect our revenue in the second half of 2015 will be comparable to the first half of the year.

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for the three and six months ended June 30, 2015 was $119.7 million and $181.6 million, respectively, compared to $56.6 million and $76.2 million for the same periods in 2014. In the second quarter of 2015, we recognized $91.2 million of revenue from our recently completed exclusive license agreement with Bayer. We also earned $56.8 million in milestone payments from our partners in the first half of 2015, which primarily consisted of:

- $41 million from Biogen for advancing ISIS-SMN$_{Rx}$ in late-stage clinical development, for advancing ISIS-BIIB4$_{Rx}$ into development and for validating two new undisclosed targets for neurological disorders; and
- $15 million from GSK for advancing the Phase 3 study of ISIS-TTR$_{Rx}$.

Our revenue in the first half of 2015 also included $26.0 million in revenue from the amortization of upfront fees and manufacturing services we performed for our partners.

Already in the third quarter of 2015, we earned $33 million from milestone payments including $22 million from Roche for the initiation of a Phase 1/2 study for ISIS-HTT$_{Rx}$ and $11 million from Biogen for continuing to advance ISIS-SMN$_{Rx}$. In the second half of 2015, we also expect to earn approximately $5 million from the amortization of the upfront payment from our new AstraZeneca collaboration, which is subject to Hart-Scott-Rodino Antitrust Improvement Act clearance.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties for the three and six months ended June 30, 2015 was $0.8 million and $1.5 million, respectively, compared to $0.4 million and $9.1 million for the same periods in 2014. The decrease in the first half of 2015 compared to the same period in 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 six months ended June 30, 2015 were $75.8 million and $147.7 million, respectively, and increased compared to $63.7 million and $121.6 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}, ISIS-SMN_{Rx}, 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 second half of the year, the costs associated with these programs will increase compared to the first half of 2015. Additionally, our operating expenses in the second half of the year will increase as Akcea continues to build the commercial infrastructure and advance the pre-commercialization activities necessary to successfully launch volanesorsen within the next couple of years. We also had an increase in stock compensation expense due to the increase in our stock price in the first half of 2015 compared to the same period in 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 June 30,		Six Months Ended June 30,	
	2015	2014	2015	2014
Isis Core	$ 54,188	$ 50,410	$ 106,256	$ 97,113
Akcea Therapeutics	7,989	5,608	14,529	9,664
Non-cash compensation expense related to equity awards	13,605	7,708	26,910	14,777
Total operating expenses	$ 75,782	$ 63,726	$ 147,695	$ 121,554

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. Non-cash compensation expense related to equity awards increased significantly in 2015 compared to 2014 primarily due to the increase in our stock price in the first half of 2015 compared to the same period in 2014.

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 June 30,		Six Months Ended June 30,	
	2015	2014	2015	2014
Research, development and patent expenses	$ 57,542	$ 52,863	$ 111,503	$ 100,438
Non-cash compensation expense related to equity awards	10,465	6,401	20,951	12,274
Total research, development and patent expenses	$ 68,007	$ 59,264	$ 132,454	$ 112,712

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2015	2014	2015	2014
Isis Core	$ 50,531	$ 47,427	$ 98,750	$ 91,123
Akcea Therapeutics	7,011	5,436	12,753	9,315
Non-cash compensation expense related to equity awards	10,465	6,401	20,951	12,274
Total research, development and patent expenses	$ 68,007	$ 59,264	$ 132,454	$ 112,712

For the three and six months ended June 30, 2015, our total research, development and patent expenses were $57.5 million and $111.5 million, respectively, compared to $52.9 million and $100.4 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):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2015	2014	2015	2014
Antisense drug discovery expenses	$ 10,654	$ 10,759	$ 21,314	$ 19,855
Non-cash compensation expense related to equity awards	2,935	1,844	5,854	3,530
Total antisense drug discovery	$ 13,589	$ 12,603	$ 27,168	$ 23,385

Antisense drug discovery costs for the three and six months ended June 30, 2015 were $10.7 million and $21.3 million, respectively, compared to $10.8 million and $19.9 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.

Antisense Drug Development

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2015	2014	2015	2014
KYNAMRO	$ 1,067	$ 620	$ 2,321	$ 2,417
ISIS-TTR$_{Rx}$	4,380	2,028	7,612	4,409
ISIS-SMN$_{Rx}$	6,211	5,473	12,331	7,436
Volanesorsen	3,816	1,957	6,187	3,011
Other antisense development products	10,330	12,909	19,466	23,690
Development overhead costs	8,429	7,157	17,101	15,580
Total antisense drug development, excluding non-cash compensation expense related to equity awards	34,233	30,144	65,018	56,543
Non-cash compensation expense related to equity awards	3,657	2,325	7,371	4,402
Total antisense drug development	$ 37,890	$ 32,469	$ 72,389	$ 60,945

Antisense drug development expenses were $34.2 million and $65.0 million for the three and six months ended June 30, 2015, respectively, compared to $30.1 million and $56.5 million for the same periods in 2014. Expenses in the first half of 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 June 30,		Six Months Ended June 30,	
	2015	2014	2015	2014
Isis Core	$ 27,584	$ 25,278	$ 53,197	$ 48,396
Akcea Therapeutics	6,649	4,866	11,821	8,147
Non-cash compensation expense related to equity awards	3,657	2,325	7,371	4,402
Total antisense drug development	$ 37,890	$ 32,469	$ 72,389	$ 60,945

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. As part of our collaboration with Genzyme, we have transitioned development responsibility for KYNAMRO to Genzyme. We and Genzyme share development costs equally until KYNAMRO is profitable.

Manufacturing and Operations

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

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2015	2014	2015	2014
Manufacturing and operations	$ 6,350	$ 5,226	$ 11,983	$ 10,992
Non-cash compensation expense related to equity awards	1,172	750	2,344	1,449
Total manufacturing and operations	$ 7,522	$ 5,976	$ 14,327	$ 12,441

Manufacturing and operations expenses were $6.4 million and $12.0 million for the three and six months ended June 30, 2015, respectively, and increased compared to $5.2 million and $11.0 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 June 30,		Six Months Ended June 30,	
	2015	2014	2015	2014
Isis Core	$ 6,180	$ 4,815	$ 11,441	$ 10,111
Akcea Therapeutics	170	411	542	881
Non-cash compensation expense related to equity awards	1,172	750	2,344	1,449
Total manufacturing and operations	$ 7,522	$ 5,976	$ 14,327	$ 12,441

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 June 30,		Six Months Ended June 30,	
	2015	2014	2015	2014
Personnel costs	$ 2,387	$ 2,385	$ 5,062	$ 4,948
Occupancy	1,887	1,819	3,720	3,554
Patent expenses	466	706	1,064	1,080
Depreciation and amortization	549	578	1,092	1,149
Insurance	326	300	638	594
Other	690	946	1,612	1,723
Total R&D support costs, excluding non-cash compensation expense related to equity awards	6,305	6,734	13,188	13,048
Non-cash compensation expense related to equity awards	2,701	1,482	5,382	2,893
Total R&D support costs	$ 9,006	$ 8,216	$ 18,570	$ 15,941

R&D support costs for the three and six months ended June 30, 2015 were $6.3 million and $13.2 million, respectively, and 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 June 30,		Six Months Ended June 30,	
	2015	2014	2015	2014
Isis Core	$ 6,113	$ 6,575	$ 12,798	$ 12,761
Akcea Therapeutics	192	159	390	287
Non-cash compensation expense related to equity awards	2,701	1,482	5,382	2,893
Total R&D support costs	$ 9,006	$ 8,216	$ 18,570	$ 15,941

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 June 30,		Six Months Ended June 30,	
	2015	2014	2015	2014
General and administrative expenses	$ 4,635	$ 3,155	$ 9,282	$ 6,339
Non-cash compensation expense related to equity awards	3,140	1,307	5,959	2,503
Total general and administrative expenses	$ 7,775	$ 4,462	$ 15,241	$ 8,842

General and administrative expenses were $4.6 million and $9.3 million for the three and six months ended June 30, 2015, respectively, and increased compared to $3.2 million and $6.3 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 June 30,		Six Months Ended June 30,	
	2015	2014	2015	2014
Isis Core	$ 3,657	$ 2,983	$ 7,506	$ 5,990
Akcea Therapeutics	978	172	1,776	349
Non-cash compensation expense related to equity awards	3,140	1,307	5,959	2,503
Total general and administrative expenses	$ 7,775	$ 4,462	$ 15,241	$ 8,842

Akcea Therapeutics, Inc.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2015	2014	2015	2014
Development expenses	$ 7,011	$ 5,436	$ 12,753	$ 9,315
General and administrative expenses	978	172	1,776	349
Total operating expenses, excluding non-cash compensation expense related to equity awards	7,989	5,608	14,529	9,664
Non-cash compensation expense related to equity awards	953	—	1,511	—
Total Akcea Therapeutics operating expenses	$ 8,942	$ 5,608	$ 16,040	$ 9,664

Expenses for Akcea Therapeutics were $8.0 million and $14.5 million for the three and six months ended June 30, 2015, respectively, and increased compared to $5.6 million and $9.7 million for the same periods in 2014. The increase in expenses was primarily due to Akcea's Phase 3 program for volanesorsen, which continues to advance, and other projects, including ISIS-APO(a)$_{Rx}$ and ISIS-ANGPTL3$_{Rx}$. Also, starting in 2015, Akcea incurred additional general and administrative costs necessary to operate, including costs to build the commercial infrastructure and advance the pre-commercialization activities necessary to successfully launch volanesorsen within the next couple of years, which will continue to increase in the second half of 2015. For 2015 and 2014, we allocated a portion of Isis' general and administrative and R&D support costs 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 six months ended June 30, 2015 was $0.9 million and $1.8 million, respectively, compared to $0.7 million and $1.3 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 the first half of 2015 compared to the same periods in 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 June 30,		Six Months Ended June 30,	
	2015	2014	2015	2014
2¾ percent notes:				
Non-cash amortization of the debt discount and debt issuance costs	$ 626	$ 1,832	$ 1,237	$ 3,638
Interest expense payable in cash	421	1,383	842	2,767
1 percent notes:				
Non-cash amortization of the debt discount and debt issuance costs	5,118	—	10,136	—
Interest expense payable in cash	1,249	—	2,499	—
Non-cash interest expense for long-term financing liability	1,665	1,654	3,327	3,306
Other	48	92	107	193
Total interest expense	$ 9,127	$ 4,961	$ 18,148	$ 9,904

Interest expense for the three and six months ended June 30, 2015 was $9.1 million and $18.1 million, respectively, compared to $5.0 million and $9.9 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. 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.

Net Income (Loss) and Net Income (Loss) per Share

Net income for the three and six months ended June 30, 2015 was $35.6 million and $18.9 million, respectively, compared to a net loss of $12.1 million and $43.4 million for the same periods in 2014. Basic net income per share for the three and six months ended June 30, 2015 was $0.30 and $0.16, respectively, compared to a basic and diluted net loss per share of $0.10 and $0.37 for the same periods in 2014. Diluted net income per share for the three and six months ended June 30, 2015 was $0.29 and $0.15. We had net income in the first half of 2015 primarily due to the revenue we earned from our exclusive license agreement with Bayer for ISIS-FXI$_{Rx}$.

Liquidity and Capital Resources

We have financed our operations with revenue primarily from research and development collaborative agreements. Additionally, we have earned revenue from the sale or licensing of our intellectual property. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From our inception through June 30, 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 June 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 June 30, 2015, we had cash, cash equivalents and short-term investments of $754.9 million and stockholders' equity of $300.3 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 June 30, 2015, we had consolidated working capital of $753.3 million, compared to $721.3 million at December 31, 2014. The increase in our cash and working capital primarily relates to the more than $165 million we received from our partners, including the $100 million up-front payment we received from Bayer. Our cash balance at June 30, 2015 did not include nearly $100 million, which is comprised of payments we have generated to date in the third quarter.

As of June 30, 2015, our debt and other obligations totaled $641.8 million compared to $643.5 million at December 31, 2014.

The following table summarizes our contractual obligations as of June 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	$ 128.6	$ 6.4	$ 13.3	$ 14.0	$ 94.9
Equipment Financing Arrangements (principal and interest payable)	$ 1.2	$ 1.1	$ 0.1	$ —	$ —
Other Obligations (principal and interest payable)	$ 1.3	$ 0.1	$ 0.1	$ 0.1	$ 1.0
Capital Lease	$ 0.1	$ 0.1	$ —	$ —	$ —
Operating Leases	$ 25.2	$ 1.8	$ 3.5	$ 3.0	$ 16.9
Total	$ 757.7	$ 16.2	$ 30.4	$ 90.8	$ 620.3

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 June 30, 2015 our outstanding convertible debt was as follows (amounts in millions unless otherwise noted):

	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 will 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 June 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 June 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 June 30, 2015, our outstanding borrowings under this loan agreement were at a weighted average interest rate of 4.18 percent. The carrying balance under this loan agreement at June 30, 2015 and December 31, 2014 was $1.2 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 June 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, ISIS-SMN$_{Rx}$ 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, ISIS-SMN$_{Rx}$ 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, ISIS-SMN$_{Rx}$ 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, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, unaffordable.

If we fail to compete effectively, our drugs, including KYNAMRO, volanesorsen, ISIS-SMN$_{Rx}$ 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, ISIS-SMN$_{Rx}$ 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, ISIS-SMN_{Rx} 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 ISIS-SMN_{Rx}.

KYNAMRO is, and, following approval any of our other drugs, including volanesorsen, ISIS-SMN_{Rx} 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, ISIS-SMN_{Rx} 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, ISIS-SMN_{Rx} 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, ISIS-SMN$_{Rx}$ 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, ISIS-SMN$_{Rx}$ 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, ISIS-SMN$_{Rx}$ 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, ISIS-SMN$_{Rx}$ 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, ISIS-SMN$_{Rx}$ 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, ISIS-SMN$_{Rx}$ 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, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$. If any of our drugs in clinical studies, including KYNAMRO, volanesorsen, ISIS-SMN$_{Rx}$ 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, ISIS-SMN$_{Rx}$ 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, ISIS-SMN$_{Rx}$ 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, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, or result in enforcement action after approval that could limit the commercial success of our drugs, including KYNAMRO, volanesorsen, ISIS-SMN$_{Rx}$ 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, ISIS-SMN_{Rx} 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, ISIS-SMN_{Rx} 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 June 30, 2015, we had an accumulated deficit of approximately $1.0 billion and stockholders' equity of approximately $300.3 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from research grants and the sale or licensing of our patents, as well as interest income. We 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, ISIS-SMN_{Rx} 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, ISIS-SMN_{Rx} 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 June 30, 2015, we had cash, cash equivalents and short-term investments equal to $754.9 million. If we do not meet our goals to successfully commercialize KYNAMRO and our other drugs, including volanesorsen, ISIS-SMN$_{Rx}$ 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, ISIS-SMN$_{Rx}$ 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 June 30, 2015, the market price of our common stock ranged from $27.37 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 June 30, 2015. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to June 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
3.1	Amended and Restated Bylaws. Filed as an exhibit to the Registrant's Current Report on Form 8-K filed with the SEC on July 2, 2015 and incorporated herein by reference.
10.1	License Agreement between the Registrant and Bayer Pharma AG dated May 1, 2015. Portions of this exhibit have been omitted and separately filed with the SEC.
10.2	Line of Credit Agreement between the Registrant and Morgan Stanley Private Bank, National Association dated June 16, 2015.
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 June 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)	August 4, 2015
/s/ Elizabeth L. Hougen Elizabeth L. Hougen	Senior Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	August 4, 2015

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

EXHIBIT 10.1

CONFIDENTIAL **EXECUTION COPY**

LICENSE AGREEMENT

BETWEEN

ISIS PHARMACEUTICALS, INC.,

AND

BAYER PHARMA AG

LICENSE AGREEMENT

This LICENSE AGREEMENT (the "***Agreement***") is entered into as of the 1st day of May, 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, USA ("***Isis***"), and **BAYER PHARMA AG**, a company organized under the laws of Germany, having its principal place of business at Muellerstraße 178, 13353 Berlin, Germany ("***Bayer***"). Bayer and Isis each may be referred to herein individually as a "***Party***" or collectively as the "***Parties***." Capitalized terms used in this Agreement, whether used in the singular or the plural, have the meaning set forth in APPENDIX 1. All attached appendices and schedules are a part of this Agreement.

RECITALS

WHEREAS, Isis has discovered and developed through human proof-of concept a novel antithrombotic drug, ISIS-FXI$_{Rx}$, based on Isis' knowledge, experience and intellectual property rights to both antisense technology and to ISIS-FXI$_{Rx}$;

WHEREAS, Isis seeks a partner with sufficient expertise in researching, developing and commercializing human therapies to enable the further development and commercialization of ISIS-FXI$_{Rx}$;

WHEREAS, Isis is conducting, and may in the future conduct, research and development of antithrombotic drugs, and may develop and commercialize such antithrombotic drugs to the extent permitted by this Agreement;

WHEREAS, Bayer has expertise in researching, developing and commercializing human therapeutics and, in particular, antithrombotic drugs, and is interested in developing and commercializing ISIS-FXI$_{Rx}$ with the assistance and input of Isis as further described herein;

WHEREAS, Bayer is conducting, and may in the future conduct, research and development in antithrombotic mechanisms, including inhibition of Factor XI, and may develop and commercialize antithrombotic drugs, including drugs whose mechanism of action is the inhibition of Factor XI;

WHEREAS, Bayer is interested in working with Isis to create a suite of antithrombotic drugs over time to complement ISIS-FXI$_{Rx}$ as further set forth herein, and is therefore interested in obtaining options from Isis to a not yet developed follow-on compound targeting Factor XI [***] utilizing new advancements to antisense technology;

WHEREAS, in pursuit of the development and commercialization of ISIS-FXI$_{Rx}$ Bayer intends to make significant upfront investments in clinical trials and to share with Isis the results of its proprietary and commercially sensitive research regarding Factor XI;

WHEREAS, Bayer desires Isis to (i) grant Bayer an exclusive license to ISIS-FXI$_{Rx}$ to enable Bayer to further develop and commercialize ISIS-FXI$_{Rx}$ under a mutually agreed strategic development and commercialization plan to optimize the global commercial value of ISIS-FXI$_{Rx}$, (ii) provide Bayer with target exclusivity with respect to ASOs targeting Factor XI, [***], and (iii) grant Bayer exclusive options to a drug discovery program to identify a follow-on development candidate targeting Factor XI [***]; and

WHEREAS, the Parties intend that they will jointly pursue the development and commercialization of ISIS-FXI$_{Rx}$, with Isis completing certain clinical and non-clinical studies that are ongoing for ISIS-FXI$_{Rx}$ as of the Execution Date and Bayer conducting all other development and all commercialization of ISIS-FXI$_{Rx}$, with the input of Isis as further described herein, where such development will initially focus on one indication for specific patient populations, and may subsequently expand development and commercialization of ISIS-FXI$_{Rx}$ to potentially include other commercially-viable indications.

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

ARTICLE 1.
DEVELOPMENT & COMMERCIALIZATION PROGRAM FOR ISIS-FXI$_{RX}$

1.1. **The Strategic Plan for ISIS-FXI**Rx. Subject to and in accordance with the terms of this Agreement, Bayer will use Commercially Reasonable Efforts to Develop and Commercialize ISIS-FXI$_{Rx}$ for an indication in [***] (the "***First Indication***") and, if it is commercially reasonable to do so, Bayer will use Commercially Reasonable Efforts to Develop and Commercialize ISIS-FXI$_{Rx}$ in Additional Indications, in each case in accordance with a global strategic development and commercialization plan (the "***Strategic Plan***").

The Strategic Plan will cover both the long-term global strategy for ISIS-FXI$_{Rx}$, the Isis Completion Activities, as well as, on a rolling [***]-month basis, the more detailed activities Bayer will perform over the course of the next [***] months. The activities and strategy in the Strategic Plan will be driven by [***].

As such, it is anticipated that the Strategic Plan will evolve over time and become more detailed (particularly with regard to Commercialization and pre-Commercialization activities) as the Products move closer to market. The Strategic Plan will, to the extent possible and useful, contain [***]. Without limiting the foregoing, *solely* to the extent Bayer has the information for its own internal purposes and in a reasonable level of detail, when updating the Strategic Plan, Bayer will include the following components:

(i) The objectives of the Strategic Plan and estimated timelines;

(ii) Indications for ISIS-FXI$_{Rx}$ (including the First Indication Bayer will pursue for ISIS-FXI$_{Rx}$) and the indications for the other Products, if any (which indications will be added to and/or refined over time);

(iii) The estimated timing and launch sequence of initial and subsequent indications for ISIS-FXI$_{Rx}$ and the other Products;

(iv) The key Clinical Studies, [***];

(v) Key elements of the manufacturing planning and strategy to support Development, Product Approvals and Commercialization; and

(vi) Key elements of the global Commercialization strategy for each Product [***], including – each on a high level basis – [***], which shall be updated [***] for a rolling [***] months outlook and [***] a year for a rolling [***] months outlook.

In addition, if Bayer exercises its Option to ISIS-FXI$_{Rx}$-2 and/or [***], those Products will be included in the Strategic Plan in accordance with the principles set forth in this Section 1.1.

1.2. **Initial Strategic Plan**. The Parties expect the initial Strategic Plan (attached hereto as APPENDIX 2) agreed to by the Parties as of the Execution Date and as further updated under this Section 1.2 will not contain all of the items and level of detail listed above in items (i) through (vi) of Section 1.1, but rather will contain the items and level of detail appropriate as of the Execution Date consistent with the level of detail Bayer uses generally for its other products at similar stages of development, [***]. Within [***] days after the Effective Date, Bayer will deliver to Isis a proposed updated Strategic Plan in accordance with Section 1.1, as applicable at an appropriate level of detail for a product in [***], and Bayer will finalize such updated Strategic Plan at the appropriate level of detail Bayer generally uses for a product in [***] within [***] days after Isis' receipt of such proposed updated plan using the process described in Section 1.3 below.

1.3. **Updating the Strategic Plan**. The initial Development activities performed by Bayer and Isis under the Strategic Plan will be designed to support market Approval and Commercialization of the First Indication of ISIS-FXI$_{Rx}$.

1.3.1. Bayer will review and update the Strategic Plan every [***] months and the Parties will meet with one another or hold a telephone conference to review such updates. In addition, the Parties may meet or hold a telephone conference more often as mutually agreed on an *ad-hoc* basis to address any urgent matters that arise with respect to Products. Each Party will ensure that its representatives at such meetings are senior development and/or commercial executives or have similar experience and expertise. Bayer will be primarily responsible for coordinating and scheduling such meetings or telephone conferences, and the Parties will mutually determine the location of meetings. Each Party will be responsible for the costs of its own representatives attending such meetings. At such meeting or telephone conference, as applicable, the Parties will discuss *inter alia*:

(i) any available new data and results from ongoing or completed Clinical Studies and non-clinical studies;

(ii) available updates regarding the progress of ongoing Clinical Studies and any New Drug Option Programs;

(iii) technology advancements potentially relevant to the Products;

(iv) changes proposed by either Party to the Strategic Plan;

(v) upcoming scientific, development or commercial events that may impact the Products;

(vi) publication plan (including the strategy for scientific publications and presentations at medical meetings); and

(vii) the evolving competitive landscape [***] and its impact on the Products and strategy.

1.3.2. **Material Changes to the Strategic Plan**. Bayer has primary responsibility for preparing each proposed updated Strategic Plan and the agenda for each meeting or telephone conference, and will submit such proposed updated plan and agenda to Isis at least [***] days prior to the date of the Parties' next scheduled meeting or telephone conference, as applicable. Any changes to the Strategic Plan materially changing [***] (each, a "***Material Change***") shall be treated in accordance with SCHEDULE 1.3.2.

In addition, at such meetings or telephone conferences Isis will have the right to review and comment on (but not approve) non-material changes to the Strategic Plan and may propose non-material changes to the Strategic Plan, and Bayer will consider Isis' comments and proposals in good faith. Bayer shall timely communicate any update of the Strategic Plan to Isis and, *provided* any Material Changes have been determined in accordance with this Section 1.3.2, then upon Isis' receipt of the updated Strategic Plan from Bayer, the updated Strategic Plan shall apply and supersede any prior versions of the Strategic Plan.

1.4. **Development of Additional Indications**. If Isis decides to request Bayer to Develop and Commercialize an Additional Indication for ISIS-FXI$_{Rx}$ that Bayer is not then currently Developing or Commercializing, Isis and Bayer shall discuss such request in good faith and either Party shall have the opportunity to conduct the commercially reasonable analysis to decide if the Development and Commercialization of such Additional Indication shall be pursued. If, after the end of such discussions and analysis, Isis and Bayer do not mutually agree that Bayer shall Develop and Commercialize such Additional Indication, Isis may formally request Bayer in writing to Develop and Commercialize such an Additional Indication for ISIS-FXI$_{Rx}$. If Bayer does not confirm to Isis in writing that Bayer will initiate the Clinical Study required for the Development of such Additional Indication for ISIS-FXI$_{Rx}$ within [***] Business Days following Bayer's receipt of Isis' request under this Section 1.4, then Isis shall have the right to conduct the Development of such Additional Indication for ISIS-FXI$_{Rx}$, unless Bayer reasonably believes in good faith and delivers a written objection to Isis detailing that [***], *provided however,* that Bayer has provided Isis with reasonable evidence documenting such issue or concern. If the prerequisites under this Section 1.4 are fulfilled and in the event the Clinical Study regarding such Additional Indication for ISIS-FXI$_{Rx}$ [***], then Bayer shall exert Commercially Reasonable Efforts to Commercialize ISIS-FXI$_{Rx}$ in such Additional Indication in the same countries Bayer is Commercializing ISIS-FXI$_{Rx}$, and shall [***]. Nothing in this Section 1.4 limits or otherwise relieves Bayer of its obligations under Section 1.1 or Section 1.6, *provided however*, that Isis [***].

1.5. Clinical Study Data Sharing.

1.5.1. Advance Notice of Upcoming SAP Data. On or about [***] days before the date a Party estimates that the data generated based on the primary database lock under the statistical analysis plan will be available for a Clinical Study such Party is conducting, such Party will provide the other Party with a written notice of such Clinical Study data event date (and a copy of any material event-related documentation), so that the Parties may prepare for their next meeting to discuss such data and plan for any potential disclosures in accordance with Section 12.4.4 or Section 12.4.5 (as applicable).

1.5.2. SAP Data Sharing. The Party conducting a Clinical Study will notify the other Party within [***] Business Days after the data generated based on the primary database lock under the statistical analysis plan is available for such Clinical Study (and, together with such notice, will provide the other Party with such available data), and the Parties will discuss the need for any potential disclosure in accordance with Section 12.4.4, and as soon as reasonably practicable (but no later than [***] days), will meet or hold a telephone conference to review and discuss such data and analyze any impact on the Strategic Plan; *provided*, *however*, that this Section 1.5.2 will not prevent either Party from fulfilling its disclosure obligations required under Applicable Law (including under Section 1.8 below).

1.6. Bayer Diligence.

1.6.1. Generally. Bayer's obligations under ARTICLE 1 (including conducting Bayer's activities set forth in the Strategic Plan), will be to use Commercially Reasonable Efforts to Develop and Commercialize Products. Bayer will [***] regarding [***] so long as such [***] are consistent with the Strategic Plan and Bayer's obligations under Section 1.6.2. Unless specifically set forth otherwise in this Agreement, Isis shall reasonably support and provide Bayer with all information and records requested by Bayer that are necessary or useful to Develop or Commercialize Products to the extent reasonably available to Isis and not already provided to Bayer with respect to Bayer's obligations under ARTICLE 1.

1.6.2. **Specific Performance Milestone Events**. Bayer will use Commercially Reasonable Efforts to achieve the specific performance milestone events set forth in SCHEDULE 1.6.2 ("***Specific Performance Milestone Events***"); *provided*, *however*, [***]. In addition, the Parties acknowledge that each of the Specific Performance Milestone Events for a given Product [***], each time the Strategic Plan is modified in accordance with this Agreement.

1.7. **Isis Completion Activities for ISIS-FXI$_{Rx}$**. In partial consideration for the up-front payment to Isis under Section 7.1, Isis will use Commercially Reasonable Efforts to complete the ongoing activities expressly set forth on SCHEDULE 1.7 for ISIS-FXI$_{Rx}$ (the "***Isis Completion Activities***"), in accordance with the timelines specified therein. Isis will [***] regarding [***] so long as such [***] are consistent with SCHEDULE 1.7. Isis only obligations regarding Development of ISIS-FXI$_{Rx}$ will be to use Commercially Reasonable Efforts to complete the Isis Completion Activities. Except for the Isis Completion Activities, Bayer will be solely responsible for the Development and Commercialization of ISIS-FXI$_{Rx}$. On a study-by-study basis, within [***] days after Isis completes a study within the Isis Completion Activities, Isis will provide Bayer [***].

1.8. **Safety Reporting; Regulatory Coordination**. The Parties agree that Bayer shall apply for and remain the IND-holder in the United States and in any other jurisdiction in which Bayer will conduct Clinical Studies for ISIS-FXI$_{Rx}$. Isis shall fully support Bayer in its application of such IND and as IND-holder in such jurisdictions and provide Bayer with all required or useful available documentation and information, including a copy of Isis' IND filed in Canada for ISIS-FXI$_{Rx}$ and the investigator brochure related to ISIS-FXI$_{Rx}$ no later than [***] days following Bayer's written request thereof. In addition, upon Bayer's reasonable request, Isis will transfer to Bayer Isis' then current global safety database established and maintained sufficient for regulatory submissions for ISIS-FXI$_{Rx}$ in an electronic (i.e., ARGUS) or written format in which Isis stores such database. The Parties agree that it is important that Isis and Bayer coordinate their respective ISIS-FXI$_{Rx}$ Clinical Studies and pre-clinical, and regulatory activities, including the collection and reporting of adverse events involving ISIS-FXI$_{Rx}$. Upon import of Isis' then current global safety database for ISIS-FXI$_{Rx}$ into Bayer's safety database, Bayer will assume responsibility for the global safety database related to Clinical Studies of ISIS-FXI$_{Rx}$. Furthermore, Bayer will be responsible for reporting to the competent Regulatory Authorities, ethics committees and investigators in accordance with the Applicable Law for expeditable adverse events and for periodic safety reporting relating to the safety of ISIS-FXI$_{Rx}$ in all applicable jurisdictions where Bayer holds an IND, Clinical Trial Application (CTA) or equivalent. Isis will continue to fulfill all sponsor obligations related to Isis' sponsored Clinical Studies, including but not limited to expedited reporting to Regulatory Authorities, ethics committees and investigators in all applicable jurisdictions where Isis holds an IND, CTA or equivalent.

1.8.1. In furtherance of the safety reporting, coordination and cooperation under this Section 1.8, as soon as reasonably practicable after the Effective Date (but in any case before Bayer Initiates a Clinical Study of ISIS-FXI$_{Rx}$), the Parties will develop and agree in writing on a drug safety information agreement (the "***Drug Safety Information Agreement***") that will include safety data exchange procedures governing the collection, investigation, reporting, and delivery of information between Bayer and Isis concerning any adverse experiences, and any product quality and product complaints involving adverse experiences related to ISIS-FXI$_{Rx}$, sufficient to enable both Parties to comply with their legal and regulatory obligations and internal processes and consistent with the terms of this Agreement.

1.8.2. Following the Effective Date and until the Drug Safety Information Agreement is executed by the Parties, Isis will promptly report to Bayer (and provide documentation to Bayer related to) any serious adverse events (SAEs), suspected unexpected serious adverse reactions (SUSARs), and any other information Bayer reasonably requires to comply with its legal and regulatory requirements inter alia as future IND-holder or sponsor of any Clinical Study conducted by or on behalf of Bayer for ISIS-FXI_{Rx}. In addition, unless explicitly set forth otherwise in the Drug Safety Information Agreement, Isis will provide Bayer with [***] updates regarding adverse events and lab findings under any Clinical Study for ISIS-FXI_{Rx} being conducted by or on behalf of Isis.

1.9. Manufacturing and Supply.

1.9.1. ISIS-FXI_{Rx} API and Finished Drug Product Manufacturing Transition Strategy. Within the first [***] days after the Effective Date and thereafter upon request of a Party, the Parties will discuss and mutually agree on a strategy to transition API and Finished Drug Product Manufacturing for ISIS-FXI_{Rx} to a Third Party CMO or Bayer's own manufacturing site. Bayer will compensate Isis in accordance with Section 7.13 for Isis' technology transfer activities associated with such transfer under a plan mutually agreed by the Parties.

1.9.2. Supplies under the Strategic Plan.

(a) Supplies for Bayer's Activities. Bayer shall provide, [***], all API and Finished Drug Product sufficient to support Bayer's activities under the Strategic Plan, *except* Isis will supply Bayer the following:

(i) API Supply. Upon Bayer's written request delivered to Isis during the first [***] months after the Effective Date, in partial consideration for the up-front payment to Isis under Section 7.1 [***], Isis will (on its own or through a CMO) supply to Bayer by a reasonable delivery date mutually agreed by the Parties (i) [***] of API (the "***Initial Supply***") ([***]) using Isis' standard form of quality agreement with such changes as mutually agreed by the Parties and in a quality complying with the provisions set forth in such quality agreement, and (ii) [***] of [***] oligonucleotides to support the activities under the Strategic Plan.

(ii) **Finished Drug Product Supply**. To support the first [***] Bayer will conduct under the Strategic Plan, upon Bayer's written request, Isis will use Commercially Reasonable Efforts to have its CMO supply Finished Drug Product (using API made by Isis or Isis' CMO) to Bayer in a quantity, quality and by a delivery date mutually agreed by the Parties that is reasonably sufficient for such [***], on the commercial terms applicable to Finished Drug Product set forth in SCHEDULE 1.9.2(a). Isis shall ensure that the supply of Finished Drug Product is accompanied by all information and documents reasonably requested by Bayer, including the analytical release data.

(b) **Supplies for the Isis Completion Activities**. Isis will provide, [***], API and Finished Drug Product sufficient to support the Isis Completion Activities.

1.9.3. **After Isis Completes the Isis Completion Activities**. After Isis completes the Isis Completion Activities set forth on SCHEDULE 1.7 for ISIS-FXI$_{Rx}$, in addition to the Initial Supply and such Finished Drug Product under Section 1.9.2, [***].

ARTICLE 2.
REQUESTS TO INITIATE NEW DRUG DISCOVERY PROGRAMS; OPTIONS

2.1. **Requests to Initiate a New Drug Discovery Program**. During the first [***] years after the Effective Date, so long as Bayer is using Commercially Reasonable Efforts to Develop and/or Commercialize at least one Product under this Agreement, Bayer may deliver to Isis a written request (each, a "***Drug Discovery Request Notice***") with the commencement fee set forth in Section 7.2 to initiate either or both of the drug discovery program(s) described below; *provided* the commencement fee for each such program is only paid once:

2.1.1. ***The ISIS-FXI***$_{Rx}$***-2 Option***. A request for Isis to initiate a drug discovery program to identify a follow-on Development Candidate targeting Factor XI incorporating Isis' then current antisense technology (such follow-on Development Candidate, "***ISIS-FXI***$_{Rx}$***-2***" and such program, the "***ISIS-FXI***$_{Rx}$***-2 Program***"); and/or

2.1.2. ***The [**\] Option***. A request for Isis to initiate a drug discovery program to identify a Development Candidate targeting [***] incorporating Isis' then current antisense technology (such Development Candidate, "[*******]" and such program, the "[*******] ***Program***").

The ISIS-FXI$_{Rx}$-2 Program and the [***] Program are each referred to as a "***New Drug Option Program***." During the [***]-year period described in this Section 2.1, at Bayer's request, Isis will meet with Bayer to update Bayer on the current state of Isis' technology and any advancement relevant to this Agreement, and will discuss the applicability of these advancements to drugs targeting Factor XI and [***]. Bayer will have the right to obtain an exclusive license to ISIS-FXI$_{Rx}$-2 and/or [***] as further described in Section 2.4 below.

2.2. New Drug Option Program Activities.

2.2.1. Development Candidate Identification Plans. After Bayer delivers a Drug Discovery Request Notice to Isis under Section 2.1, the Parties will discuss [***]. For each New Drug Option Program, Isis will provide Bayer an initial draft plan to identify a Development Candidate under the applicable New Drug Option Program (the "***Development Candidate Identification Plan***"). Bayer will review such plan with Isis and the Parties will agree on a final Development Candidate Identification Plan for such New Drug Option Program. Isis will use Commercially Reasonable Efforts to complete the activities for each New Drug Option Program set forth in the applicable Development Candidate Identification Plan [***] in a manner consistent with its internal practices for other gene targets with the goal of identifying a Development Candidate for the applicable New Drug Option Program as soon as possible. If the Parties cannot mutually agree on a final Development Candidate Identification Plan for a given New Drug Option Program, Isis will perform such New Drug Option Program under a plan consistent with Isis' other plans to create Development Candidates for other gene targets in Isis' own internal programs. Bayer may propose changes to the Development Candidate Identification Plan, and Isis will consider Bayer's comments and proposals in good faith [***] regarding the conduct of the Development Candidate Identification Plan so long as [***].

2.2.2. Third Party Obligations Applicable to Development Candidates. While the Parties are reviewing technology options for the Development Candidate to be used under a Development Candidate Identification Plan, the Parties will discuss any Third Party Obligations they believe apply to such technology. Isis will disclose to Bayer any Third Party Obligations known by Isis that apply to technology under consideration by the Parties, [***]. Any Third Party Obligations arising under agreements Isis has with Third Parties covering [***] that Bayer agrees to incorporate into the Development Candidate under the Development Candidate Identification Plan, will be [***] (such technology, collectively "***Bayer Opt-In Technology***"). All other Third Party Obligations that [***] as a result of technology that is *not* Bayer Opt-In Technology used in a Development Candidate under the applicable Development Candidate Identification Plan will be [***]. Isis will update APPENDIX 4 to reflect any additional agreements Isis has with Third Parties covering such Bayer Opt-In Technology.

2.2.3. New Drug Option Program Development Candidate Selection. Isis will notify Bayer in writing promptly after Isis has designated a Lead Candidate for a given New Drug Option Program and, together with such notice, Isis will provide Bayer [***]. Bayer will then have the opportunity to determine, by the Option Deadline, whether the Lead Candidate [***] will be selected as the Development Candidate.

2.3. **New Drug Option Program Term**. The period during which Isis will perform the activities under a New Drug Option Program will begin on the date Isis receives the applicable Drug Discovery Request Notice and will end on the earlier of the date (i) Isis completes the activities Isis agreed to perform under the applicable Development Candidate Identification Plan, or (ii) the Parties [***] (such period, a "***New Drug Option Program Term***").

2.4. **Options**. On a New Drug Option Program-by-New Drug Option Program basis, beginning on the date Isis receives the applicable Drug Discovery Request Notice under Section 2.1 and ending on or before 5:00 p.m. (Eastern Time) on the later of (y) the [***] day (each, an "***Option Deadline***") following Bayer's receipt of [***] for such New Drug Option Program or – if applicable – (z) [***] Business Days following the date on which antitrust clearance for the exercise of the Option (as defined below) has been obtained (using the process described in Section 13.6, *mutatis mutandis*, under which the Parties will make the appropriate filings under the HSR Act within [***] days after Bayer's receipt of [***] for such New Drug Option Program), Bayer will have an exclusive option (each, an "***Option***") to obtain from Isis the license set forth in Section 5.1.2 or Section 5.1.3 (as applicable); *provided, however*, [***]. Bayer will determine whether to select the Lead Candidate [***] as the Development Candidate, and will notify Isis whether Bayer is exercising its Option to license the applicable Development Candidate from such New Drug Option Program by notifying Isis in writing on or before the applicable Option Deadline.

2.4.1. If, by the Option Deadline, Bayer (i) notifies Isis in writing that Bayer has selected a Development Candidate and is exercising the Option for a particular New Drug Option Program, and (ii) pays Isis – subject to prior antitrust clearance (if applicable) – the license fee in accordance with Section 7.3 for the applicable New Drug Option Program, Isis will, and hereby does, grant to Bayer the license set forth in Section 5.1.2 or Section 5.1.3 (as applicable).

2.4.2. If, by the Option Deadline for a particular New Drug Option Program, Bayer has not both (i) selected a Development Candidate and provided Isis a written notice stating that Bayer is exercising the Option, and (ii) paid Isis the license fee in accordance with Section 7.3 for the applicable New Drug Option Program, then Bayer's Option with respect to such New Drug Option Program will expire. In such a case, subject to Section 4.1, Bayer will have no further rights to (and Isis will have no further obligations with respect to) such New Drug Option Program (including all Compounds included in the applicable New Drug Option Program).

2.5. **Expiration of New Drug Option Program Term**.

2.5.1. **Effects of Expiration of New Drug Option Program Term**. On a New Drug Option Program-by-New Drug Option Program basis, if by the expiration of the applicable New Drug Option Program Term, Isis has not – after having consulted with Bayer – designated in good faith a Lead Candidate under a particular New Drug Option Program, then, subject to Section 2.5.2, the Option will expire and such program will no longer be a New Drug Option Program under this Agreement. Following expiration of any unexercised Option for a New Drug Option Program, subject to Section 2.5.2 and to Isis' exclusivity covenants under Section 4.1, (i) Isis will own any Compounds discovered under such New Drug Option Program and will be free to Develop and Commercialize such Compounds on its own or with a Third Party; (ii) Isis will own all data, results, Patent Rights and information generated under the New Drug Option Program and Bayer will upon Isis' request promptly transfer to Isis all such data, results, Patent Rights and information in Bayer's possession; and; (iii) the Parties' will no longer have an obligation to perform any activities under this ARTICLE 2 with respect to such New Drug Option Program.

2.5.2. **Carryover Development Candidates**. If, by the expiration of the applicable New Drug Option Program Term for a particular New Drug Option Program, Isis has not designated a Lead Candidate for such New Drug Option Program in accordance with Section 2.5.1, and at any time during the [***]-month period after the end of the applicable New Drug Option Program Term Isis designates an ASO discovered by Isis that is designed to bind to the RNA that encodes the Exclusive Target for such New Drug Option Program as a development candidate (such ASO, a "***Carryover Development Candidate***"), then, Isis will notify Bayer and will provide Bayer with [***], and Bayer will have an exclusive option ("***Carryover Option***") to obtain from Isis the license under Section 5.1.2 or Section 5.1.3 (as applicable) [***], *except* the applicable option deadline will be deemed extended such that it begins on the date Bayer receives [***] and ends at 5:00 p.m. (Eastern Time) on the [***] Business Day thereafter (such period, the "***Carryover Option Deadline***"). The Carryover Option Deadline may be extended, if requested by Bayer, in the same manner as the Option Deadline as described in Section 2.4.

If Bayer's Carryover Option expires unexercised, then, subject to Isis' exclusivity obligations under Section 4.1 [***], Bayer will have no further rights to (and Isis will have no further obligations with respect to) such Carryover Development Candidate (including all Compounds included in the applicable New Drug Option Program); *provided*, *however*, [***].

2.6. **New Drug Option Program Development Plans – After Option Exercise**. With respect to each Development Candidate for which Bayer has exercised its Option in accordance with Section 2.4 or Section 2.5.2 above, the Parties will promptly integrate such Development Candidate into the Strategic Plan in accordance with Section 1.3 above at the next scheduled meeting or telephone conference of the Parties following such Option exercise. The components of the Strategic Plan applicable to such Development Candidate will be consistent with Section 1.1 and Bayer's Specific Performance Milestone Events and estimated timelines set forth in SCHEDULE 1.6.2.

ARTICLE 3.
PROGRAM MANAGEMENT AND COSTS

3.1. **Alliance Managers; Meeting Participation**. If the Parties mutually agree that it would be beneficial to progress the activities under this Agreement, each Party may appoint a representative to act as its alliance manager (each, an "***Alliance Manager***"). Each Alliance Manager will be responsible for performing the activities listed in SCHEDULE 3.1. Except as set forth in Section 6.2 (if requested by the other Party to so attend the meeting), Section 8.1.3(c) (if the Parties mutually agreed to establish a JPC) or in Schedule 1.3.2, Isis has the right, but not the obligation, to attend any meetings described in this Agreement (including the meetings described in ARTICLE 1), and may discontinue attending such meetings at any time after providing written notice to Bayer. For clarity, Isis shall not be entitled to attend any Bayer internal meetings (including internal meetings with Bayer's Sublicensees or contractors).

3.2. **Records and Quality; Inspections; Materials Transfer**.

3.2.1. **Records**. Each Party will maintain records consistent with its own practice of all work such Party performs under this Agreement and all results, data, inventions and developments made in the performance of such work. Such records will be in sufficient detail and in good scientific manner appropriate for patent and regulatory purposes. Upon prior written notice, a Party will provide the other Party with copies of all requested records, to the extent reasonably required for the performance of a Party's rights and obligations under this Agreement.

3.2.2. **Inspections**. Each Party will cooperate in good faith with respect to the conduct of any inspections by any Regulatory Authority of a Party's site or a Party's contractor's site and facilities if such inspection concerns work being performed under this Agreement. Each Party will be given the opportunity to attend any inspections by any Regulatory Authority of the other Party's or such Party's contractor's site and facilities with one of its representatives if such inspections concern work being performed under this Agreement, and the summary (or wrap up) meeting with a Regulatory Authority at the conclusion of such site inspection unless the Regulatory Authority expresses its preference that such other Party should not participate in such meetings. If, during that inspection of the Party's facilities, a Regulatory Authority finds such facilities to be non-compliant with one or more GLP, GMP, GCP or current standards for pharmacovigilance practice compliance standards and such facilities are being used to conduct work under this Agreement, such Party will promptly notify the other Party of such finding and will submit a proposed recovery/corrective action plan, including a time line for implementation of the plan, within [***] days of such notification of non-compliance.

3.2.3. **Materials Transfer**. In order to facilitate the activities under this Agreement, either Party may provide to the other Party certain materials for use by the other Party in furtherance of the activities to be performed under this Agreement. Unless agreed otherwise between the Parties, 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. Except as expressly agreed in writing between the Parties before or after the Effective Date, SUCH 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.

3.3. Program Costs.

3.3.1. Isis Completion Activities.

(a) Except as otherwise provided under Section 3.3.1(b), Isis will be responsible for all costs associated with [***], including any costs associated with [***].

(b) If Bayer requests any changes to the Isis Completion Activities which are [***] and Isis agrees to implement such changes, then [***]. Isis and Bayer will update SCHEDULE 1.7 with any such revised activities.

3.3.2. Strategic Plan. Bayer will be responsible for all costs associated with [***] under the Strategic Plan.

3.3.3. Development Candidate Identification Plan Costs.

(a) **Isis Activities**. Isis will be responsible for all costs associated with the activities Isis agrees to perform under each Development Candidate Identification Plan; *provided*, since Factor XI [***] as of the Execution Date, if the Parties mutually agree [***] under Isis' plans to create development candidates for other previously validated gene targets in Isis' own internal programs, Bayer will [***] in accordance with [***].

(b) **Bayer Activities**. Bayer will be responsible for any costs associated with [***] under each Development Candidate Identification Plan.

ARTICLE 4.
EXCLUSIVITY COVENANTS

4.1. Exclusivity Covenants.

4.1.1. Isis' and Bayer's Exclusivity Covenants. Isis and Bayer each acknowledge and agree that, during the Agreement Term, and subject to the exclusivity granted in Section 5.1, each Party may, independently or for or with any of its Affiliates (including with Third Party academic collaborators and other independent contractors for the sole benefit of such Party or its Affiliate), conduct Research with an ASO that is designed to bind to the RNA that encodes Factor XI or [***]. Except in the performance of its obligations or exercise of its rights under this Agreement and except as set forth in Section 4.1.2, Section 4.1.3 or Section 4.2, Isis [***] will not work independently or for or with any of its Affiliates or any Third Party (including the grant of any license to any Third Party) with respect to:

(a) The Drug Discovery, Development or Commercialization of an ASO that is designed to bind to the RNA that encodes Factor [***], until the [***] anniversary of the Effective Date; and

(b) After the [***] anniversary of the Effective Date, on a country-by-country basis, Commercializing an ASO that is designed to bind to the RNA that encodes Factor XI [***], so long as Bayer is Developing or Commercializing a Product under this Agreement [***];

provided, however, in no way will Section 4.1.1(a) or Section 4.1.1(b) permit Isis to Commercialize a Product in violation of Bayer's exclusive license to such Product under Section 5.1.1, Section 5.1.2 or Section 5.1.3 (as applicable).

As of the Effective Date, Isis does not have (nor intends to have) an internal Drug Discovery program for Factor XI incorporating Isis' latest antisense technology.

4.1.2. Isis-Products. Notwithstanding the provisions of Section 4.1.1, on a New Drug Option Program-by-New Drug Option Program basis, if (A) Bayer does not ask Isis to identify a Development Candidate for such New Drug Option Program under Section 2.1 by the [***] anniversary of the Effective Date, or (B) Bayer timely asks Isis to identify a Development Candidate for such New Drug Option Program under Section 2.1 but either (a) no Lead Candidate has been designated by the end of the New Drug Option Program Term in accordance with Section 2.5.1, or (b) Bayer either does not (X) timely exercise its Option with respect to such Development Candidate, or (Y) use Commercially Reasonable Efforts to continue to Develop and Commercialize such Development Candidate, then, subject - in the case of [***] - to Section 4.2, (i) each Party (for itself or with or for a Third Party) will be permitted to conduct Research, Drug Discovery and Develop an ASO (and, solely in the case of Isis, such Development Candidate) designed to bind to the RNA that encodes such Exclusive Target that is not the Product being developed by Bayer (an "***Isis-Product***"), (ii) after expiration of the Full Royalty Period for ISIS-FXI_{Rx} in a country, Isis will be permitted to Commercialize an Isis-Product that encodes Factor XI in such country, and (iii) after expiration of the Full Royalty Period for [***] (if any) in a country, Isis will be permitted to Commercialize an Isis-Product that encodes [***] in such country.

4.1.3. **Limitations and Exceptions to Isis' Exclusivity Covenants**. Notwithstanding anything to the contrary in this Agreement, Isis' practice of the following will not violate ARTICLE 4:

(i) Any activities pursuant to the Prior Agreements as in effect on the Effective Date as described on APPENDIX 8;

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

(iii) Any activities pursuant to Section 4.2 below.

4.2. **Isis' Right to Initiate a New Drug Option Program for [***]**. Notwithstanding any provision to the contrary in this Agreement, if Isis intends to initiate a program to conduct Drug Discovery and Develop an ASO that is designed to bind to the RNA that encodes [***] ("[*******] ***Program"***) before the date Bayer delivers Isis a Drug Discovery Request Notice under Section 2.1, then the following provisions shall apply:

(a) Promptly after Isis has designated a [***] as a lead candidate ready to start [***] in accordance with the principles for the Lead Candidate set forth in ARTICLE 2, Isis will provide written notice to Bayer of such designation and together with such notice shall provide Bayer with documentation corresponding in content and detail to [***]. Upon receipt of such documentation, Bayer shall have [***] days to decide whether it wishes to participate in the [***] Program, and if Bayer chooses [***] to participate in such [***] Program, the provisions regarding [***] shall apply as if Bayer had submitted a Drug Discovery Request Notice under Section 2.1.2 with respect to [***] (and after Option exercise, such [***] shall constitute [***] under this Agreement);

(b) If Bayer does not timely notify Isis under Section 4.2(a) above of Bayer's decision to participate in the [***] Program, Isis may proceed with the Drug Discovery and Development of the [***] subject to the terms of this Section 4.2;

(c) During the course of such Drug Discovery and Development activities with the [***], Isis shall provide Bayer with periodic (at least [***]) updates of progress of such Drug Discovery and Development;

(d) If Isis conducts any Clinical Studies of the [***] before the date Bayer delivers to Isis a Drug Discovery Request Notice under Section 2.1 or exercises its Option pursuant to Section 4.2(e) then, in addition to the periodic updates provided for in Section 4.2(c), Isis shall, within [***] days following Completion of each such Clinical Study provide Bayer with the data generated based on the primary database lock under the statistical analysis plan for such Clinical Study in order to assist Bayer with its decision of whether to exercise its Option to the [***]. In addition, Isis shall provide Bayer with any additional information and data in Isis' possession that Bayer reasonably requests;

(e) Unless Bayer's Option to [***] has already expired unexercised under Section 2.4, at any time until 5:00 pm (Eastern Time) on the [***] anniversary of the Effective Date, Bayer may exercise its Option to the [***];

(f) If Bayer timely exercises its Option to the [***] and timely pays Isis the license fee for the [***] in accordance with Section 7.3.2, then Isis will grant Bayer the license set forth in Section 5.1.3. In addition, within [***] days after such Option exercise (and Bayer's receipt of an invoice from Isis), Bayer shall pay Isis [***] of the total amount of [***] that Isis incurred in Developing the [***] up to the date of such Option exercise; *provided, however*, that [***];

(g) If Bayer does not timely exercise its Option to the [***] in accordance with Section 2.4 or this Section 4.2, then, Isis shall have the right to further Develop and Commercialize the [***] and, subject to Section 4.2(h), Bayer will have no further rights to (and Isis will have no further obligations with respect to) the [***] (including all Compounds included in the applicable New Drug Option Program);

(h) For the avoidance of doubt, none of the foregoing affects (A) Bayer's obligation to pay Isis any payments with respect to [***] that [***] Option exercise under this Section 4.2, including the license fee under Section 7.3.2, the milestone payments under Section 7.6 and Section 7.7.3, and royalties under Section 7.9, or (B) Bayer's rights to deliver to Isis a Drug Discovery Request Notice to request initiation of a [***] Program pursuant to Section 2.1 of this Agreement.

(i) Isis hereby covenants as of the Effective Date that it will not during the Agreement Term grant any right or license to any Third Party that would conflict with the rights granted to Bayer under this Section 4.2 and that it will not take any action that would conflict with or adversely affect its obligations to Bayer under this Section 4.2.

4.3. **Effect of Exclusivity on Indications**. The Compounds and Products are designed to bind to the RNA that encodes Factor XI or [***] in the Field, which are known to play a role in [***]. Isis and Bayer are subject to exclusivity obligations under Section 4.1.1; *however*, the Parties acknowledge and agree that each Party (on its own or with a Third Party) may continue to discover, research, develop, manufacture and commercialize products which are not covered by the exclusivity obligations under Section 4.1.1, including ASOs that are designed to bind to the RNA that encodes a gene that is ***not*** an Exclusive Target for any indication, even if such products are designed to treat [***].

ARTICLE 5.
LICENSE GRANTS; TECHNOLOGY TRANSFER AND SUPPORT

5.1. License Grants to Bayer.

5.1.1. ISIS-FXI$_{Rx}$ Development, Manufacture and Commercialization License. Subject to the terms and conditions of this Agreement, Isis hereby grants to Bayer a worldwide, exclusive, royalty-bearing license under the Licensed Technology to Research, Develop, Manufacture, have Manufactured and Commercialize ISIS-FXI$_{Rx}$ in the Field.

5.1.2. ISIS-FXI$_{Rx}$-2 Development, Manufacture and Commercialization License. Subject to the terms and conditions of this Agreement, effective upon Bayer's exercise of the Option for ISIS-FXI$_{Rx}$-2 in accordance with Section 2.4, or Section 2.5.2, Isis grants to Bayer a worldwide, exclusive, royalty-bearing license under the Licensed Technology to Research, Develop, Manufacture, have Manufactured and Commercialize ISIS-FXI$_{Rx}$-2 in the Field.

5.1.3. [*******] **Development, Manufacture and Commercialization License**. Subject to the terms and conditions of this Agreement, effective upon Bayer's exercise of the Option for [***] in accordance with Section 2.4, Section 2.5.2, or Section 4.2 Isis grants to Bayer a worldwide, exclusive, royalty-bearing license under the Licensed Technology to Research, Develop, Manufacture, have Manufactured and Commercialize [***] in the Field.

5.1.4. Sublicense Rights. Bayer may only grant sublicenses under the licenses granted to Bayer in Section 5.1 as expressly permitted by this Section 5.1.4.

(a) Right to Grant Sublicenses. Bayer acknowledges that the licenses under Section 5.1 are personal to Bayer and are granted to Bayer due to Bayer's strong development and commercialization experience with therapeutics to treat [***]. Therefore, to help ensure that a partner of similar quality and experience as Bayer will continue to diligently Develop and Commercialize the Products, Bayer will only have the right to grant sublicenses under the licenses granted under Section 5.1.1, Section 5.1.2 and Section 5.1.3 above:

(i) under the Licensed Technology to an Affiliate of Bayer to Research, Develop, Manufacture, have Manufactured and Commercialize a Product in the Field; or

(ii) under the Licensed Technology to a Bayer alliance partner for purposes of further Development, Manufacturing and Commercialization of a Product in the Field [***] if [***], *provided* Bayer gives Isis [***] days advance written notice of such sublicense; or

(iii) under the Isis Core Technology Patents, Isis Product-Specific Patents, Isis Manufacturing and Analytical Patents and Isis Manufacturing and Analytical Know-How solely to [***]; or

(iv) in all other cases with Isis' prior written consent (which consent will not be unreasonably withheld, conditioned or delayed), under the Licensed Technology to a Third Party solely for purposes of further Research, Manufacturing, Development and Commercialization of a Product in the Field;

provided that each such sublicense will be subject to, and consistent with, the terms and conditions of this Agreement.

(b) **Enforcement of Sublicense Agreements**. If, within [***] days after first learning of any breach of the terms of any such sublicense agreement, Bayer fails to take any action to enforce the sublicense terms of a sublicense granted pursuant to this Section 5.1.4, which failure would cause a material adverse effect on Isis, Bayer will cooperate with and support Isis (which cooperation will be at Bayer's sole reasonable expense and will include, Bayer 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. Bayer will provide Isis with a copy of any sublicense granted pursuant to this Section 5.1.4 within [***] days after the execution thereof; *provided*, *however*, Bayer may redact any information in such sublicense that does not pertain to Products.

(c) **CMO Agreements**. In connection with Bayer's selecting and engaging one or more CMOs to supply API or Finished Drug Product for Development or Commercialization, Isis will grant, at Bayer's request, a [***] license from Isis to [***] under the [***] to the extent necessary for [***], *provided however*, [***]. Isis shall use Commercially Reasonable Efforts to conclude a respective license agreement with [***] within [***] days following Bayer's request thereof. If and to the extent [***] requires further sublicenses under the Licensed Technology to Manufacture API or Finished Drug Product for the Development or Commercialization of Product, any prior written approval required by Bayer under Section 5.1.4(a)(iv) shall be deemed received upon conclusion of a license agreement between Isis and [***]. In addition, if Bayer intends to [***], then Isis will [***]. Isis and Bayer shall use Commercially Reasonable Efforts to [***] within [***] days following [***].

(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 Bayer; *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 Bayer, 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 Bayer. Bayer agrees that it will confirm clause (i) of the foregoing in writing at the request and for the benefit of Isis or if requested by the Sublicensee.

5.1.5. **Consequence of Natural Expiration of this Agreement**. If this Agreement naturally expires in accordance with Section 11.1 then, in addition to the terms set forth in Section 11.3.1(c), Section 11.3.1(e), Section 11.3.1(g) and Section 11.3.1(h), Isis will and hereby does grant to Bayer a perpetual, nonexclusive, worldwide, royalty-free license under the Licensed Know-How to Research, Develop, Manufacture, have Manufactured and Commercialize the Product that is the subject of such expiration.

5.1.6. **No Implied Licenses**. All rights in and to Licensed Technology not expressly licensed to Bayer under this Agreement are hereby retained by Isis or its Affiliates. All rights in and to Bayer Technology not expressly licensed or assigned to Isis under this Agreement, are hereby retained by Bayer 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.

5.1.7. **License Conditions; Limitations**. Subject to Section 7.11, the licenses granted under Section 5.1.1, Section 5.1.2 and Section 5.1.3 and the sublicense rights under Section 5.1.4 are subject to and limited by (i) the Prior Agreements and (ii) the Isis In-License Agreements, in each case to the extent the provisions of such obligations or agreements are specifically disclosed to Bayer in this Agreement, including its Schedules (x) prior to the Execution Date, with respect to ISIS-FXI$_{Rx}$ and/or the Licensed Patents Covering ISIS-FXI$_{Rx}$, or (y) in writing prior to Bayer's exercise of the applicable Option, with respect to ISIS-FXI$_{Rx}$-2 or [***] and/or the Licensed Patents Covering ISIS-FXI$_{Rx}$-2 or [***].

5.1.8. **Trademark and Domain Names**

(a) Bayer shall be solely responsible for the selection, registration and maintenance of the Trademarks which it employs in connection with the Commercialization of the Products. Bayer shall own and control the Trademarks and pay all relevant costs related thereto.

(b) Isis recognizes the exclusive ownership by Bayer of any proprietary Bayer Marks, logotype, Trademarks or Trade Dress furnished by Bayer (e.g. the name "Bayer" and the "Bayer Cross") for use in connection with the Commercialization of the Products. Isis shall not, either during the Agreement Term, or at any time thereafter, register, use or challenge or assist others to challenge the Trademark, the Bayer Marks, logotype and trade dress furnished by Bayer or attempt to obtain any right in or to any such name, logotype, Trademarks or Trade Dress confusingly similar for the marketing of the Product or any other goods and products, irrespective of the fact that such goods or products have a different use or are dissimilar to the Product.

(c) Only Bayer will be authorized to initiate at its own discretion legal proceedings against any infringement or threatened infringement of the Trademarks.

(d) Bayer shall be responsible for the registration, hosting, maintenance and defense of the Domain Names under all generic Top Level Domains (gTLDs) and under all relevant country code Top Level Domains (ccTLD). For the avoidance of doubt Bayer is allowed to register such Domain Names in its own name, to host on its own servers, maintain and defend the Domain Names and use them for websites.

5.1.9. **Subsequently Acquired Formulation Technology or Delivery Devices**. On a Product-by-Product basis, if Isis Controls any Formulation Technology or delivery device that would be useful with a Product, Isis will notify Bayer of such technology and will discuss in good faith with Bayer the terms under which Isis would be willing to grant Bayer a license under such technology for use with such Product.

5.2. **Assignment of Certain Licensed Patents; Grant Back to Isis**.

5.2.1. ***Certain Licensed Patents Covering ISIS-FXI***$_{Rx}$. With respect to ISIS-FXI$_{Rx}$, when Bayer pays Isis the milestone payment for Completion of the CS IV Study, following Bayer's written request and review and consideration by each Party's patent representatives and, *except* as otherwise provided in Section 5.2.3, Isis will assign to Bayer, Isis' ownership interest in (i) all Isis Product-Specific Patents Covering ISIS-FXI$_{Rx}$ that are owned by Isis (whether solely owned or jointly owned with one or more Third Parties), and (ii) all Jointly-Owned Program Patents Covering ISIS-FXI$_{Rx}$, and thereafter, except as otherwise provided in Section 8.2.3, Bayer will be fully responsible for the Prosecution and Maintenance of such Isis Product-Specific Patents and such Jointly-Owned Program Patents and Bayer will use Commercially Reasonable Efforts to Prosecute and Maintain such Patent Rights. The assignment of Patent Rights assigned in this Section 5.2.1 will occur within [***] days after Bayer's request.

5.2.2. ***Certain Licensed Patents Covering ISIS-FXI***$_{Rx}$***-2 and/or*** **[***]**. If Bayer (a) exercises its Option for ISIS-FXI$_{Rx}$-2 or [***] (as applicable), and (b) together with such Option exercise notice, elects to have Isis commence the assignment under this Section 5.2.2, then following the review and consideration by each Party's patent representatives and, *except* as otherwise provided in Section 5.2.3, Isis will assign to Bayer, Isis' ownership interest in (i) all Isis Product-Specific Patents Covering such Product that are owned by Isis (whether solely owned or jointly owned with one or more Third Parties), and (ii) all Jointly-Owned Program Patents Covering such Product, and thereafter, except as otherwise provided in Section 8.2.3, Bayer will be fully responsible for the Prosecution and Maintenance of such Isis Product-Specific Patents and such Jointly-Owned Program Patents and Bayer will use Commercially Reasonable Efforts to Prosecute and Maintain such Patent Rights. The assignment of Patent Rights assigned in this Section 5.2.2 will occur within [***] days after Bayer's written notice to Isis under Section 7.3 of Bayer's election to have Isis commence such assignment.

5.2.3. Notwithstanding the foregoing, if either Party reasonably determines that the assignment contemplated under Section 5.2.1 or Section 5.2.2 would be likely to adversely affect the applicable Licensed Patent (including diminishing the scope, term, validity or enforceability of such Licensed Patent), or otherwise at Bayer's request (and on payments made pursuant to Section 7.3), then, in lieu of such assignment, Bayer will retain its exclusive license to such Licensed Patent under Section 5.1.

5.2.4. Bayer grants to Isis a fully-paid, royalty-free (except to the extent Section 7.10 requires a royalty on a Discontinued Product), worldwide, non-exclusive, sublicensable license under any Isis Product-Specific Patents and Jointly-Owned Program Patents assigned to Bayer under Section 5.2.1 and Section 5.2.2, (i) for [***], (ii) to complete the Isis Completion Activities and any activities under a New Drug Option Program, and (iii) to conduct the activities permitted by Section 4.1.2 or Section 4.2.

5.2.5. For purposes of clarification, any Isis Product-Specific Patents and Jointly-Owned Program Patents assigned to Bayer under Section 5.2.1 and Section 5.2.2 are royalty-bearing and will still be considered Licensed Patents Covering the applicable Product for determining the royalty term and applicable royalty rates under ARTICLE 7.

5.3. **Subcontracting**. Subject to the terms of this Section 5.3, each Party may engage Third-Party subcontractors to perform its obligations under this Agreement. Any subcontractor engaged by a Party 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 such a subcontractor will remain responsible for such activities and will not grant rights that interfere with the other Party's rights under this Agreement. Notwithstanding the foregoing sentence, each Party shall at all times have the right to engage its Affiliates to perform its obligations under this Agreement.

5.4. **Technology and Information Transfer**. Isis will (i) promptly, but no later than [***] days following the date (y) Bayer pays Isis the milestone payment for [***], in the case of the Licensed Know-How licensed to Bayer under Section 5.1.1, or (z) on a New Drug Option Program-by-New Drug Option Program basis, the license under Section 5.1.2 or Section 5.1.3 (as applicable) is granted to Bayer with respect to the Development Candidate for such New Drug Option Program, and (ii) during the Agreement Term promptly following Bayer's reasonable request deliver to Bayer the following Licensed Know-How:

5.4.1. **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 5.1.1, Section 5.1.2 or Section 5.1.3, as the case may be, to Bayer, which includes, for ISIS-FXI_{Rx}, (i) the information included in the IND, and (ii) the data from the Phase 1 Clinical Trials and Phase 2 Clinical Trials conducted by Isis, together with all regulatory documentation.

5.4.2. **Isis Manufacturing and Analytical Know-How**. Solely for use by Bayer, its Affiliates or a Third Party acting on Bayer's behalf to Manufacture API in Bayer's own [***] 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 Bayer, [***] of the Manufacturing rights granted under Section 5.1.1, Section 5.1.2 or Section 5.1.3, as the case may be.

5.4.3. **Isis Assistance**. If requested by Bayer, Isis will provide Bayer with a timely and reasonable level of assistance in connection with such Licensed Know-How under Section 5.4.1 and Section 5.4.2, and Bayer will reimburse Isis for its time incurred in providing such assistance in accordance with Section 7.13.

5.5. **Cross-Licenses under Program Technology**.

5.5.1. **Enabling Patent Licenses from Bayer to Isis**. Subject to the terms and conditions of this Agreement (including Isis' exclusivity obligations under Section 4.1 and without limiting the license(s) granted to Bayer under Section 5.1), Bayer hereby grants Isis a fully-paid, royalty-free, irrevocable, worldwide, non-exclusive, sublicensable license under any Bayer Program Technology (excluding any Product-Specific Patents) to Research, Develop, manufacture, have manufactured and Commercialize [***]; *provided*, *however*, that Isis will not have the right to use or grant a sublicense to a Third Party under any [***] or [***] included within such Bayer Program Technology for any Bayer Excluded Indication. For purposes of this Section 5.5.1, "***Bayer Excluded Indication***" means [***] (such notification to be in writing together with a list of such Bayer Excluded Indications).

5.5.2. **Enabling Patent Licenses from Isis to Bayer**. Subject to the terms and conditions of this Agreement (including Bayer's exclusivity obligations under Section 4.1 and without limiting the license(s) granted to Bayer under Section 5.1), Isis hereby grants Bayer a fully-paid, royalty-free, irrevocable, worldwide, non-exclusive, sublicensable license under any Isis Program Technology (excluding any Product-Specific Patents) to Research, Develop, manufacture, have manufactured and Commercialize [***]; *provided, however*, that Bayer will not have the right to use or grant a sublicense to a Third Party under any [***] or [***] included within such Isis Program Technology for any Isis Excluded Indication. For purposes of this Section 5.5.2, "***Isis Excluded Indication***" means [***] (such notification to be in writing together with a list of such Isis Excluded Indications).

ARTICLE 6.
REGULATORY MATTERS AND THE ISIS INTERNAL ASO SAFETY DATABASE

6.1. **Investigator's Brochure**. Bayer will keep Isis reasonably informed with respect to the status, activities and progress of Development of Products licensed by Bayer hereunder by providing updated versions of the investigator's brochure to Isis [***] and when Development of the Products results in any substantive change to the safety or risk to the Products.

6.2. **Participation in Regulatory Meetings**. Prior to any scheduled meeting with a Regulatory Authority regarding a Product [***] (i) the Parties will discuss the timing and objectives for such meeting, and (ii) the Party who is the IND-holder will provide the other Party with an opportunity to discuss the strategy for such meeting with the IND-holder it being understood that the IND-holder shall have the right to set the timeline for such discussions between the Parties and that the IND-holder shall have the final decision-making authority regarding [***]. In addition, the IND-holder will allow the other Party to participate [***] in any such meeting with a Regulatory Authority [***] as an [***] unless the Regulatory Authority expresses its preference that such other Party should not participate in such meeting. Upon request of the IND-holder the respective other Party shall participate in any meetings with the Regulatory Authority and at all times support the IND-holder in a timely manner with respect to its obligations under this Section 6.2.

6.3. **Regulatory Communications**. The Party who is the IND-holder will provide the other Party with a draft of all material correspondence with and submissions to any Regulatory Authority [***], sufficiently in advance of providing such correspondence or submission to the applicable Regulatory Authority to enable the other Party [***]. The contents of such correspondence or submission to any Regulatory Authority will reflect the applicable aspects of the Strategic Plan. The IND-holder will have the final decision-making authority regarding the contents of all such correspondence or submissions but [***]. Upon request of the IND-holder the respective other Party shall timely support the IND-holder at all times with respect to its obligations under this Section 6.3.

6.4. **Class Generic Claims**. To the extent Bayer intends to make any claims in a Product label or regulatory filing that are class generic to ASOs, Isis' generation 2.0 or 2.5 chemistry platform(s), Conjugate Technology, or any other Isis technology included in a Product, Bayer will provide such claims and regulatory filings to Isis in advance and will consider in good faith any proposals and comments made by Isis.

6.5. **Applicable Laws**. Each Party will perform its activities pursuant to this Agreement (and will use reasonable efforts to require Third Parties to perform any such activities) in compliance with good laboratory practices (GLP), good clinical practices (GCP), and good manufacturing practices (GMP), in each case as applicable under the laws and regulations of the country and the state and local government wherein such activities are conducted or which are otherwise affected, in particular through the Commercialization of Products.

6.6. **The Isis Internal ASO Safety Database**.

(a) Isis maintains an internal database that includes information regarding the tolerability of its drug compounds, individually and as a class, including information discovered during pre-clinical and clinical development (the "***Isis Internal ASO Safety Database***"). In an effort to maximize understanding of the safety profile and pharmacokinetics of Isis compounds, Bayer will reasonably cooperate in connection with populating the Isis Internal ASO Safety Database. To the extent collected by Bayer and in the form in which Bayer stores such information for its own purposes, Bayer will provide Isis with information concerning toxicology, pharmacokinetics, safety pharmacology study(ies) and adverse events related to Products licensed by Bayer under this Agreement within a reasonable period of time. In connection with any reported serious adverse event, Bayer will provide Isis all serious adverse event reports. In addition, with respect to Products, Bayer will provide Isis with copies of Annual safety updates filed with each IND and the safety sections of any final Clinical Study reports within [***] days following the date such information is filed, as applicable. Furthermore, Bayer will provide in a timely manner to Isis any supporting data reasonably related to such safety information provided by Bayer under this Section 6.6(a) and answer any follow-up questions reasonably requested by Isis to the extent such data and answers are reasonably available to Bayer. All such information disclosed by Bayer to Isis will be Bayer Confidential Information; *provided*, *however*, that so long as Isis does not disclose the identity of a Product or Bayer's identity, Isis may disclose any such Bayer Confidential Information to (i) Isis' other partners pursuant to Section 6.6(b) below if such information is regarding class generic properties of ASOs, (ii) any Third Party (other than a Regulatory Authority) that [***], or (iii) a Regulatory Authority. Bayer 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). Bayer will also cause its Affiliates to comply with this Section 6.6(a), and will cause its Sublicensees to comply with this Section 6.6(a) with respect to all major Clinical Studies conducted by or on behalf of such Sublicensee.

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

(c) [***], Bayer may submit written requests to Isis for Isis to run queries of the Isis Internal ASO Safety Database relevant to Products licensed to Bayer under this Agreement, and Isis will use Commercially Reasonable Efforts to promptly run such queries and deliver to Bayer the results of such queries. Any information disclosed between the Parties under this Section 6.6(c) will be treated as Confidential Information in accordance with ARTICLE 12 below.

ARTICLE 7.
FINANCIAL PROVISIONS

7.1. **Up-Front Fee**. Within 10 Business Days after the Effective Date and following Bayer's receipt of an invoice from Isis (not to be sent to Bayer prior to the Effective Date), Bayer will pay Isis an up-front fee equal to $100,000,000 as follows:

(a) [***] in consideration for the exclusive license granted to Bayer under the Licensed Patents and Licensed Know-How for ISIS-FXI_{Rx};

(b) [***] in consideration for Isis' agreement to [***]; and

(c) [***] in consideration for the [***] of API and [***] oligonucleotides Isis agrees to supply to Bayer under Section 1.9.2(a)(i).

7.2. **New Drug Option Program Commencement Fees**. If Bayer delivers a Drug Discovery Request Notice to Isis under Section 2.1 stating that Bayer requests Isis to initiate a drug discovery program to identify a Development Candidate for a New Drug Option Program in accordance with this Agreement, then within [***] days following Bayer's receipt of an invoice from Isis (such invoice not to be sent prior to Isis' receipt of such Drug Discovery Request Notice) Bayer will pay Isis:

7.2.1. a fee of [***] if such Drug Discovery Request Notice is to initiate such New Drug Option Program for ISIS-FXI$_{Rx}$-2; and

7.2.2. a fee of [***] if such Drug Discovery Request Notice is to initiate such New Drug Option Program for [***].

7.3. **New Drug Option Program License Fees**.

7.3.1. **License Fee for ISIS-FXI$_{Rx}$-2**. If Bayer timely delivers written notice to Isis under Section 2.4 or Section 2.5.2 (as applicable) that Bayer is exercising the Option for ISIS-FXI$_{Rx}$-2 and (if applicable) antitrust clearance for ISIS-FXI$_{Rx}$-2 has been obtained (using the process described in Section 13.6, *mutatis mutandis*), then within [***] days following Bayer's receipt of an invoice from Isis, Bayer will pay Isis a license fee of [***]. Bayer will include in such written notice whether or not Bayer elects under Section 5.2.2 to have all Isis Product-Specific Patents and all Jointly-Owned Program Patents for ISIS-FXI$_{Rx}$-2 assigned to Bayer in accordance with Section 5.2.2. If Bayer does not provide Isis such a written notice that Bayer elects to have Isis assign such Patent Rights to Bayer in accordance with Section 5.2.2, then within [***] days following Bayer's receipt of an invoice from Isis, Bayer will pay Isis a fee of [***] as consideration for the Maintenance and Prosecution of such Isis Product-Specific Patents and Jointly-Owned Program Patents for ISIS-FXI$_{Rx}$-2.

7.3.2. **License Fee for [***]**. If Bayer timely delivers written notice to Isis under Section 2.4, Section 2.5.2 or Section 4.2 (as applicable) that Bayer is exercising the Option for [***] and (if applicable) antitrust clearance for [***] has been obtained (using the process described in Section 13.6, *mutatis mutandis*), then within [***] days following Bayer's receipt of an invoice from Isis, Bayer will pay Isis a license fee of [***]. Bayer will include in such written notice whether or not Bayer elects under Section 5.2.2 to have all Isis Product-Specific Patents and all Jointly-Owned Program Patents for [***] assigned to Bayer in accordance with Section 5.2.2. If Bayer does not provide Isis such a written notice that Bayer elects to have Isis assign such Patent Rights to Bayer in accordance with Section 5.2.2, then within [***] days following Bayer's receipt of an invoice from Isis, Bayer will pay Isis a fee of [***] as consideration for the Maintenance and Prosecution of such Isis Product-Specific Patents and Jointly-Owned Program Patents for [***].

7.4. **Milestone Payments for Achievement of Development Milestone Events by ISIS-FXI$_{Rx}$**. Bayer will pay to Isis within [***] days following Bayer's receipt of an invoice from Isis, the milestone payments as set forth in TABLE 1 below when a development milestone event listed in TABLE 1 is first achieved by ISIS-FXI$_{Rx}$:

TABLE 1	
Development Milestone Event	**Milestone Event Payment**
45 days following Bayer's receipt of the Completion Notice regarding Completion of the CS IV Study and Bayer not having delivered a notice of termination to Isis under Section 11.2.1 during such 45-day period.	$55,000,000
[***]	[***]

7.5. **Milestone Payments for Achievement of Development Milestone Events by ISIS-FXI$_{Rx}$-2**. Bayer will pay to Isis within [***] days following Bayer's receipt of an invoice from Isis, the milestone payments as set forth in TABLE 2 below when a development milestone event listed in TABLE 2 is first achieved by ISIS-FXI$_{Rx}$-2:

TABLE 2	
Development Milestone Event	**Milestone Event Payment**
[***]	[***]
[***]	[***]

7.6. **Milestone Payments for Achievement of Development Milestone Events by [***]**. Bayer will pay to Isis within [***] days following Bayer's receipt of an invoice from Isis, the milestone payments as set forth in TABLE 3 below when a development milestone event listed in TABLE 3 is first achieved by [***]:

TABLE 3	
Development Milestone Event	**Milestone Event Payment**
[***]	[***]
[***]	[***]
[***]	[***]

7.7. **Milestone Payments for Achievement of First Commercial Sale Milestone Events by a Product**.

7.7.1. ***ISIS-FXI$_{Rx}$ or ISIS-FXI$_{Rx}$-2***. Upon the earlier to occur of (i) First Commercial Sale of ISIS-FXI$_{Rx}$ [***], or (ii) First Commercial Sale of ISIS-FXI$_{Rx}$-2 [***], Bayer will pay to Isis within [***] days following Bayer's receipt of an invoice from Isis, a one-time milestone payment equal to [***].

7.7.2. ***ISIS FXI*$_{Rx}$-*2***. Bayer will pay to Isis within [***] days following Bayer's receipt of an invoice from Isis, a one-time milestone payment equal to [***], if (i) ISIS-FXI$_{Rx}$ achieves First Commercial Sale [***], and (ii) ISIS-FXI$_{Rx}$-2 achieves First Commercial Sale [***].

7.7.3. **[*****]**. Bayer will pay to Isis within [***] days following Bayer's receipt of an invoice from Isis, a one-time milestone payment equal to [***], upon achievement of First Commercial Sale of [***].

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

7.8.1. Each milestone payment set forth in TABLE 1, TABLE 2, TABLE 3 and Section 7.7 above will be paid only once upon the first achievement of the milestone event by the applicable Product regardless of how many times such Product achieves such milestone event.

7.8.2. If a particular milestone event is not achieved by a Product, then upon achievement of a later milestone event by such Product the milestone event payment applicable to such earlier milestone event will also be due.

7.8.3. If a particular milestone event is achieved by a Product contemporaneously with or in connection with another milestone event by such Product, then both milestone events will be deemed achieved and the milestone payments for both milestone events are due.

7.8.4. Each time a milestone event is achieved under this ARTICLE 7, Bayer will send Isis, or Isis will send Bayer, as the case may be, a written notice thereof within [***] Business Days following the date of achievement of such milestone event. Bayer will use good faith efforts to provide Isis advanced notice orally or in writing (including email) of any anticipated achievement of a milestone event under this ARTICLE 7.

7.9. **Royalty Payments to Isis**. As partial consideration for the rights granted to Bayer hereunder, subject to the provisions of this Section 7.9 (including the minimum royalty required under Section 7.9.3(f)(ii)), Bayer will pay to Isis royalties on the Annual worldwide Gross Margin of Products sold by Bayer, its Affiliates or Sublicensees, on a country-by-country basis in accordance with this Section 7.9. On a country-by-country basis, for each Calendar Quarter during the Full Royalty Period, royalties will be calculated as follows:

[***]	[***]	[***]	[***]	[***]

The Bayer Base Royalty Rate is calculated in accordance with Section 7.9.1 below and the applicable Regional Adjustment is calculated in accordance with Section 7.9.2 below.

7.9.1. **Bayer Base Royalty Rate**. The Bayer Base Royalty Rate will be used to calculate the royalty payment based on Gross Margin derived from Annual worldwide Net Sales of Products according to TABLE 4 below (the "***Bayer Base Royalty Rate***"):

TABLE 4

Royalty Tier	Annual Worldwide Net Sales of Products	Bayer Base Royalty Rate
1	For the portion of Annual Worldwide Net Sales ≤ [***]	[***]%
2	For the portion of Annual Worldwide Net Sales > [***] but ≤ [***]	[***]%
3	For the portion of Annual Worldwide Net Sales > [***] but ≤ [***]	[***]%
4	For the portion of Annual Worldwide Net Sales > [***]	[***]%

(a) Annual worldwide Net Sales will be calculated by taking the aggregate sum of Net Sales of all Products for all countries worldwide. For example, if Annual worldwide Net Sales of Products are [***], then the Bayer Base Royalty Rate would be [***]. As an additional example, if Annual worldwide Net Sales of Products are [***], then the Bayer Base Royalty Rate would be [***].

(b) Bayer will pay Isis royalties on Gross Margin of Products arising from pre-Approval sales, including named patient and other similar programs under Applicable Laws where Bayer, its Affiliate or Sublicensee sells such Product to a Third Party, and Bayer will provide reports and payments to Isis consistent with Section 7.14.2. No royalties are due on Gross Margin 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 or other similar programs will not be considered a First Commercial Sale for purposes of calculating the Full Royalty Period or determining whether a milestone event is achieved in Section 7.7 above.

7.9.2. **Regional Adjustment**. A specific adjustment (each, a "***Regional Adjustment***") will be used for each of the following four regions (each, a "***Region***") to calculate the actual royalty rate (each, a "***Regional Royalty Rate***") Bayer will pay Isis on Gross Margin of Products sold by Bayer, its Affiliates or Sublicensees in countries within such Region: the Region consisting of the [***] (the "[***] ***Region***"), the Region consisting of [***] (the "[***] ***Region***"), the Region consisting of [***] (the "[***] ***Region***"), and the Region consisting of [***] (the "[***] ***Region***").

(a) [***] ***Region***. The Regional Adjustment for the [***] equals [***]% such that there is no [***]; and

(b) [***] ***Region,*** [***] ***Region and the*** [***] ***Region***. On a Calendar Quarter-by-Calendar Quarter basis, the Regional Adjustment for the [***] Region, the [***] Region and the [***] Region is calculated by using the following formula: [***](the "***Average Regional Price***"), [***] (the "***Average*** [***] ***Price***") [***]. The foregoing calculation is illustrated as follows:

[***]	[***]	[***]	[***]	[***]	
[***]	[***]	[***]	[***]	[***]	

Provided:

(i) In no event will the Regional Adjustment for such [***] Region, [***] Region and the [***] Region be greater than [***]% or less than [***]%;

(ii) If, in a given Calendar Quarter, the Average Regional Price in the [***] Region, the [***] Region or the [***] Region for Product is higher than [***], then the Regional Adjustment for such [***] Region, [***] Region or the [***] Region (as applicable) for such Calendar Quarter will be [***]%; and

(iii) If, in a given Calendar Quarter, there are Product sales in the [***] Region, the [***] Region or the [***] Region but not in the [***] Region, then the Regional Adjustment for such [***] Region, [***] Region or the [***] Region (as applicable) for such Calendar Quarter will be [***]% until there are sales of such Product in the [***] Region.

7.9.3. **Application of Royalty Rates**. All royalties set forth under Section 7.9 are subject to the provisions of this Section 7.9.3, and are payable as follows:

(a) **Full Royalty Period**. Except as otherwise set forth in Section 7.9.3(b), Bayer's obligation to pay Isis the Regional Royalty Rates 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 (except as stated in Section 7.9.1(b)) of such Product until the later of the date of expiration (i) of the last Valid Claim within the Orange Book Patents (or the foreign equivalent or counterpart of such Orange Book Patents) exclusively licensed by Isis to Bayer under Section 5.1 (but excluding any Jointly-Owned Program Patents that are not Product-Specific Patents) Covering such Product in the country in which such Product is made, used or sold, (ii) of the data exclusivity period conferred by the applicable Regulatory Authority in such country with respect to such Product, and (iii) in consideration for the valuable Licensed Know-How exclusively licensed to Bayer under Section 5.1 and Isis' exclusivity covenants in Section 4.1, the [***] anniversary of the First Commercial Sale of such Product in such country (such royalty period, the "***Full Royalty Period***").

(b) **Competition from Generic Products for Products**. On a Generic Country-by-Generic Country and Product-by-Product basis, if at any time after [***], a Generic Product is sold in such Generic Country, then Bayer may deliver written notice to Isis electing to use the Generic Product reduced royalty adjustment set forth in this Section 7.9.3(b) for a given Generic Country in lieu of the applicable Regional Adjustment applicable to such country. If Bayer delivers such a written notice to Isis then in lieu of the applicable Regional Adjustment applicable to such country, (i) Bayer will pay Isis royalties on the Gross Margin of Products sold by Bayer, its Affiliates and Sublicensees in such Generic Country equal to [***].

In any Generic Country for which Bayer has elected to use the Generic Product reduced royalty adjustment under this Section 7.9.3(b), on a Calendar Quarter-by-Calendar Quarter basis, the applicable "***Generic Royalty Quotient***" will be calculated by [***].

(c) **Reduced Royalty**. Bayer acknowledges that Isis' contribution (and the value Bayer is deriving) under this Agreement is not limited to the exclusive licenses granted to Bayer under the Licensed Patent Rights, but also includes exclusive licenses to the Licensed Know-How, which contains critically valuable Know-How created and compiled by Isis from its antisense platform technology and over 25 years of experience discovering, researching, and developing ASOs, including important pre-clinical data, clinical data, and, in the case of ISIS-FXI$_{Rx}$, a robust Phase 2 clinical data package, the broad exclusivity covenants Isis is providing under Section 4.1, and (upon Bayer's request) the assignment of certain Licensed Patents to Bayer under Section 5.2.1 and Section 5.2.2. Therefore, subject to Section 7.9.3(f) and subject to Bayer's right to calculate royalties in accordance with the Generic Royalty Quotient in a Generic Country in lieu of calculating royalties using the Royalty Quotient under this Section 7.9.3(c), on a country-by-country basis, after the expiration of the Full Royalty Period and until the end of the Reduced Royalty Period, in lieu of the applicable full Regional Royalty Rate for such country, Bayer will pay Isis royalties (the "***Bayer Reduced Royalty***") on Gross Margin of Products where the applicable royalty rate is calculated on a Calendar Year-by-Calendar Year basis by [***]; *provided, however*, that the Bayer Reduced Royalty rate in each country will in no event exceed the [***].

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

(e) **Royalty Examples**. SCHEDULE 7.9.3(E) attached hereto contains examples of how royalties will be calculated under this Section 7.9.

(f) **Limitation on Aggregate Reduction for Bayer Royalties**.

(i) In no event will the aggregate royalty reductions under Section 7.9.2(b), Section 7.9.3(b), or Section 7.9.3(c) reduce the royalties payable to Isis on Gross Margin of a Product in any given period to an amount that is less than the [***].

(ii) Notwithstanding any provision to the contrary in this Agreement, in no event will the royalties payable to Isis during the Full Royalty Period under this Section 7.9 be less than [***]% of worldwide Net Sales.

(iii) In no event will the aggregate offsets under Section 7.11 reduce the royalties payable to Isis on Gross Margin of a Product in any given period to an amount that is less than the greater of [***].

7.10. **Reverse Royalty Payments to Bayer for a Discontinued Product**.

7.10.1. **Reverse Royalty for a Discontinued Product**. If Isis or any of its Affiliates or Sublicensees Commercializes a Discontinued Product, then following the First Commercial Sale of such Discontinued Product by Isis or its Affiliates or Sublicensees, Isis will pay Bayer a royalty of [***]% of Annual worldwide Net Sales of such Discontinued Product ("***Reverse Royalties***"). Isis' obligation to pay Bayer Reverse Royalties will [***].

7.10.2. **Applicable Royalty Provisions**. In addition to this Section 7.10, the definition of "*Net Sales*" in APPENDIX 1 and the other provisions contained in this ARTICLE 7 governing payment of royalties from Bayer to Isis will govern the payment of Reverse Royalties from Isis to Bayer under this Section 7.10, *mutatis mutandis*, including the provisions of Sections 7.9.3, 7.11, 7.14, 7.15, 7.16, and 7.17.

7.11. **Third Party Payment Obligations**. Other than Bayer Opt-In Technology, any Third Party Obligations that become payable by Isis or Bayer under an agreement such Party has entered into to license or otherwise acquire Third Party Patent Rights will be paid by a Party or shared by the Parties as expressly set forth in this Section 7.11.

7.11.1. **Existing In-License Agreements**.

(a) ***Isis' Existing In-License Agreements***. Certain of the Licensed Technology Controlled by Isis as of the Effective Date licensed to Bayer under Section 5.1.1 or that may be licensed to Bayer under Section 5.1.2 or Section 5.1.3, as the case may be, are in-licensed or were acquired by Isis under the agreements with Third Party licensors or sellers listed on APPENDIX 4 (such license or purchase agreements being the "***Isis In-License Agreements***"), and certain milestone, royalty payments, license maintenance fees and other payments 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 Bayer, its Affiliate or Sublicensee under this Agreement. Any payment obligations arising under the Isis In-License Agreements for Third Party Patent Rights that would be considered:

(i) Isis Core Technology Patents or Isis Manufacturing and Analytical Patents hereunder, will be paid by [***] as [***], and

(ii) Isis Product-Specific Patents hereunder, will be [***] as [***] and [***].

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

7.11.2. **New In-Licensed Isis Core Technology Patents, Isis Manufacturing and Analytical Patents or Isis Product-Specific Patents**.

(a) ***New In-Licensed Isis Core Technology Patents***. If after the Effective Date, Isis obtains Third Party Patent Rights necessary to Develop, Manufacture or Commercialize a Product that would have been considered an Isis Core Technology Patent or an Isis Manufacturing and Analytical Patent had Isis Controlled such Patent Rights on the Effective Date, Isis will include such Third Party Patent Rights in the license granted to Bayer under Section 5.1.1 for ISIS-FXI$_{Rx}$, under Section 5.1.2 for ISIS-FXI$_{Rx}$-2 or Section 5.1.3 for [***] and any and all costs arising under such Third Party agreement as they apply to Product will be paid solely by [***] as [***].

(b) ***New In-Licensed Isis Product-Specific Patents***. If after the Effective Date, Isis obtains Third Party Patent Rights necessary to Develop, Manufacture or Commercialize a Product that would have been considered an Isis Product-Specific Patent had Isis Controlled such Patent Rights on the Effective Date, Isis will include such Third Party Patent Rights in the license granted to Bayer under Section 5.1.1 for ISIS-FXI$_{Rx}$ under Section 5.1.2 for ISIS-FXI$_{Rx}$-2 or Section 5.1.3 for [***] and any and all costs arising under such Third Party agreement as they apply to Product will be [***].

7.11.3. Additional Core IP In-License Agreements.

(a) Bayer will promptly provide Isis written notice of any Additional Core IP Bayer believes it has identified and Isis will have the first right, but not the obligation, to negotiate with, and obtain a license from the Third Party Controlling such Additional Core IP. If Isis obtains such a Third Party license, Isis will include such Additional Core IP in the license granted to Bayer under Section 5.1.1, Section 5.1.2, or Section 5.1.3 (as applicable), and [***] will pay any financial obligations under such Third Party agreement as [***].

(b) If, however, Isis elects not to obtain such a license to such Third Party intellectual property, Isis will so notify Bayer, and Bayer may obtain such a Third Party license and Bayer may offset an amount equal to [***]% of any [***] paid by Bayer under such Third Party license against any [***].

(c) If it is unclear whether certain intellectual property identified by Bayer pursuant to Section 7.11.3(a) is Additional Core IP under Section 7.11.3(b), Isis will send written notice to such effect to Bayer, 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 Bayer is permitted to [***]. The costs of any Third Party expert engaged under this Section 7.11.3(c) will be paid by the Party against whose position the Third Party lawyer's determination is made.

7.12. Other Third Party Payments.

7.12.1. Isis' Third Party Agreements. Except as otherwise expressly agreed to by Bayer under Section 7.11.1 or Section 7.11.2, after Bayer is granted the applicable license under Section 5.1 for a particular Product, Bayer will be responsible for paying [***]% of the [***] arising under any Third Party agreements entered into by Isis where [***], [***].

7.12.2. Bayer's Third Party Agreements. Without limiting any applicable [***] under Section 7.11.3(b), Bayer will be responsible for paying [***]% of the [***] arising under any Third Party agreements entered into by Bayer as they apply to Products.

7.13. Invoices. If the Parties explicitly refer to this Section 7.13, for any mutually agreed work performed by Isis at Bayer's request under this Agreement (other than the Isis Completion Activities) after the first [***] hours of Isis' time, Bayer will pay Isis as a lump sum within [***] days from the date an invoice is received by Bayer; *provided that* any invoiced costs are for fees or services that have been rendered by Isis plus out-of-pocket costs incurred by Isis. Isis' invoices will include Isis' good faith estimate of the FTE cost incurred by Isis in performing the services and the amount of any out-of-pocket costs incurred and charged by Isis. Before Isis commences work, Bayer and Isis will agree to a budget for the work Bayer requests Isis to perform that will include Isis' good faith estimate of the FTE cost plus any out-of-pocket costs.

7.14. Payments.

7.14.1. Commencement. Beginning with the Calendar Quarter in which the First Commercial Sale for a Product is made and for each Calendar Quarter thereafter, Bayer will make royalty payments to Isis under this Agreement based on the Preliminary Royalty Report for the applicable Calendar Quarter within [***] days following Bayer's receipt of an invoice from Isis.

7.14.2. Reports. After the First Commercial Sale of a Product, within [***] days after the end of the most recently completed Calendar Quarter, Bayer will provide Isis with both the preliminary report and the reconciled report as described in greater detail below:

(a) Bayer shall send to Isis a preliminary royalty report summarizing Gross Margin for Products during the most recently completed Calendar Quarter on a country-by-country and Product-by-Product basis and the calculation of royalties due thereon, including sales price, Gross Margin, Bayer's Cost of Goods Sold, the exchange rate used, total sales, total units sold, if applicable the calculation of the Regional Adjustment used for each Region and any adjustment made in a Generic Country (including the calculation used for such Generic Country adjustment and all components of such calculation), or an estimate of any portions of the items set forth in the first sentence of this Section 7.14.2(a) where actuals are not known as of such time (the "***Preliminary Royalty Report***"). If no royalties are payable in respect of a given Calendar Quarter, Bayer will submit a written royalty report to Isis so indicating. 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 [***] Business Days following the end of each such Calendar Quarter, Bayer will provide Isis a [***] report estimating the Gross Margin and total Net Sales of, and royalties payable to Isis for, Products sold for such Calendar Quarter.

(b) Bayer shall send to Isis a reconciled royalty report summarizing Gross Margin for Products during the Calendar Quarter prior to the most recently completed Calendar Quarter on a country-by-country and Product-by-Product basis and the calculation of royalties due thereon, including sales price, Gross Margin, Bayer's Cost of Goods Sold, the exchange rate used, total sales, total units sold, if applicable the calculation of the Regional Adjustment used for each Region and any adjustment made in a Generic Country (including the calculation used for such Generic Country adjustment and all components of such calculation) (the "***Reconciled Royalty Report***"). In addition, following the royalty payments made by Bayer to Isis on the basis of the respective Preliminary Royalty Reports, the Reconciled Royalty Report shall state any payments due by one Party to the other Party. If the royalty payments made by Bayer to Isis on the basis of a Preliminary Royalty Report is less than the royalty payments owed by Bayer to Isis according to the applicable Reconciled Royalty Report for the applicable Calendar Quarter, Bayer shall pay to Isis the difference between such amounts as part of Bayer's next payment to Isis, and if the royalty payments made by Bayer to Isis on the basis of a Preliminary Royalty Report is more than the royalty payments owed by Bayer to Isis according to the applicable Reconciled Royalty Report for the applicable Calendar Quarter, Bayer will have a credit against any royalties due to Isis in an amount equal to the difference between such amounts (or to the extent there will be no future royalties due, then in lieu of such credit, Isis will make a payment to Bayer in an amount equal to the overpaid amount). The Parties acknowledge and agree that the Reconciled Royalty Report for the fourth Calendar Quarter in a given Calendar Year will reconcile the actual Gross Margin for Products as compared to the estimated Gross Margin for Products for both such fourth Calendar Quarter and for such entire Calendar Year.

7.14.3. **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 Sections 7.14.2(b) and 7.15), irrevocable and non-refundable. Gross Margin in currencies other than USD will be converted into USD using the average exchange rate for the applicable month as for Bayer's internal accounting and reporting process, consistently applied across Bayer's business for Bayer's pharmaceutical products.

7.14.4. **Payment Rule**. If the terms for a particular payment are not otherwise set out in this Agreement, such payment shall be made by Bayer according to the following rule: If invoices are received by Bayer at the address set forth in this Section 7.14.4 by the [***] day of the current month, then payments shall be made by the [***] day of the [***]. If invoices are received by Bayer at the below address after the [***] day [***], then payments shall be made by the [***] day of the [***]. For example, if Isis submits an invoice to Bayer and such invoice is received by Bayer on [***], then Bayer will pay such invoice by [***]. All invoices referred to in this ARTICLE 7 shall be made in compliance with Applicable Law.

All invoices shall be sent to the following address:

Bayer Pharma AG
Rechnungseingangsstelle c/o
[***]
51368 Leverkusen Germany

7.14.5. **Bank Account**. All payments made by Bayer to Isis under the Agreement shall be made by wire transfer to the following bank account of Isis, or such other United States bank account as notified by Isis to Bayer in a timely manner from time to time:

Account Holder: Isis Pharmaceuticals, Inc.
Bank: [***]
Bank Address: [***]
Account Number: [***]
Routing & Transit Number: [***]
SWIFT (BIC): [***]

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

7.15. **Audits**. No more frequently than [***] during [***] during the Agreement Term and for a period of [***] months thereafter, at the request and expense of Isis, Bayer will permit an independent certified public accountant of nationally recognized standing appointed by Isis (to whom Bayer has no reasonable objection), and with at least [***] days advance notice, during normal business hours, accompanied by a Bayer representative at all times, to examine such records as are necessary to verify the calculation and reporting of Gross Margin and the correctness of any royalty payment made under this Agreement for any period within the preceding [***] months – [***] (except in the case of fraud, in which case Isis may audit earlier periods to the extent the relevant records are available) -including, on a Region-by-Region and Product-by-Product basis, the calculation of the applicable Regional Adjustment and any adjustment due to a Generic Product entering a Generic Country, and information relevant to total sales, total units sold, average price in the Region versus average price in the United States and the applicable royalty rate used in such Region. As a condition to examining any records of Bayer, such auditor will sign a nondisclosure agreement reasonably acceptable to Bayer. Any records of Bayer examined by such accountant will be deemed Bayer's Confidential Information. Upon completion of the audit, the accounting firm will provide both Parties with a written report disclosing whether the royalty payments made by Bayer are correct or incorrect and the specific details concerning any discrepancies ("***Audit Report***"). If the Audit Report shows that Bayer's payments under this Agreement were less than the royalty amount that should have been paid, then Bayer will pay Isis the difference between such amounts to eliminate any discrepancy revealed by said inspection within [***] Business Days of receiving the Audit Report and following Bayer's receipt of an invoice from Isis, with interest calculated under Section 7.17. If the Audit Report shows that Bayer's payments under this Agreement were greater than the royalty amount that should have been paid, then [***]. Isis will pay for such audit, except that if Bayer is found to have underpaid Isis by more than [***]% of the amount that should have been paid, Bayer will reimburse Isis' reasonable costs of the audit.

7.16. **Taxes**.

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

7.16.2. **VAT**. The prices set forth in this ARTICLE 7, including its Schedules do not include Value Added Tax. If Value Added Tax is legally owed by Isis, Value Added Tax applies and will be invoiced additionally by Isis and has to be paid by Bayer to Isis after receipt of a correct invoice, which meets all legal requirements according to the Applicable Law. Any refunds of such Value Added Tax shall be to the account of Bayer and Isis shall provide all reasonable assistance as requested by Bayer in obtaining any such refunds.

7.16.3. **Withholding Tax**. The Parties agree to cooperate with one another and use reasonable efforts to lawfully avoid or reduce tax withholding or similar obligations in respect of royalties, milestone payments, and other payments made by the paying Party to the receiving Party under this Agreement. To the extent the paying Party is required to deduct and withhold taxes, interest or penalties on any payment, the paying Party will pay the amounts of such taxes to the proper governmental authority for the account of the receiving Party and remit the net amount to the receiving Party in a timely manner. The paying Party will furnish the receiving Party with proof of payment of such taxes in due course. Any withheld tax shall be treated as having been paid by paying Party to receiving Party for all purposes of this Agreement. 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.

7.16.4. **Tax Cooperation**. Isis will provide Bayer with any and all tax forms that may be reasonably necessary in order for Bayer to lawfully not withhold tax or to withhold tax at a reduced rate under an applicable bilateral income tax treaty. Following Bayer's timely receipt of such tax forms from Isis and the confirmation of German tax authorities for tax exemption (if necessary), Bayer will not withhold tax or will withhold tax at a reduced rate under an applicable bilateral income tax treaty, if appropriate under the Applicable Law. Isis will provide any such tax forms to Bayer upon request and in advance of the due date. Each Party will provide the other with reasonable assistance to determine if any taxes are applicable to payments under this Agreement and to enable the recovery, as permitted by Applicable Law, of withholding taxes resulting from payments made under this Agreement, such recovery to be for the benefit of the Party who would have been entitled to receive the money but for the application of withholding tax under this Section 7.16.

The provisions of this Section 7.16 are to be read in conjunction with the provisions of Section 13.4 below.

7.17. **Interest**. Any payments due under this Agreement shall be due on such date as specified in the Agreement. Any failure by Bayer to make a payment within ten (10) days after the date when due shall obligate Bayer to pay interest on the due payment to Isis. The interest period shall commence on the due date (inclusive) and end on the payment date (exclusive). Interest shall be calculated based on the actual number of days in the interest period divided by 360. The interest rate per annum shall be equal to the one (1) month US Libor rate, currently published on Reuters screen <LIBOR01>, fixed two Business Days prior to the due date and reset to the prevailing one (1) month US Libor rate in monthly intervals thereafter, plus a premium of [***], or shall be equal to an interest rate according to Law, whatever is lower.

ARTICLE 8.
INTELLECTUAL PROPERTY

8.1. **Ownership**.

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

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

8.1.3. **Joint Patent Committee**.

(a) If the Parties mutually agree, the Parties may establish a "***Joint Patent Committee***" or "***JPC***." If such a JPC is formed, the JPC will serve as the primary contact and forum for discussion between the Parties with respect to intellectual property matters arising under this Agreement, and will cooperate with respect to the activities set forth in this Section 8.1.3. If the JPC is not formed or it dissolves, each Party may designate a patent attorney who will be responsible for intellectual property matters under this Agreement. A strategy will be discussed with regard to (i) prosecution and maintenance, defense and enforcement of Isis Product-Specific Patents that would be or are licensed to Bayer under Section 5.1 in connection with a Product and Bayer Product-Specific Patents, (ii) defense against allegations of infringement of Third Party Patent Rights, (iii) licenses to Third Party Patent Rights or Know-How, and (iv) the timing and subject matter of any potential publications regarding a Product, in each case to the extent such matter would be reasonably likely to have a material impact on the Agreement or the licenses granted hereunder, which strategy will be considered in good faith by the Party entitled to prosecute, enforce and defend such Patent Rights, as applicable, hereunder, but will not be binding on such Party.

(b) In addition, any Joint Patent Committee (or the Parties' respective patent representatives if no JPC exists) will be responsible for the assessment of inventorship of Program Patents in accordance with United States patent laws. In case of a dispute in the Joint Patent Committee (or otherwise between Isis and Bayer) over inventorship of Program Patents, if the Joint Patent Committee (or the Parties' respective patent representatives if no JPC exists) cannot resolve such dispute, such dispute will be resolved by independent patent counsel not engaged or regularly employed in the past two years by either Party and reasonably acceptable to both Parties. The decision of such independent patent counsel will be binding on the Parties. Expenses of such patent counsel will be shared equally by the Parties.

(c) If the Parties form a JPC, it will comprise an equal number of at most three members from each Party. The Joint Patent Committee will meet as often as agreed by them (and at least semi-Annually), to discuss matters arising out of the activities set forth in this Section 8.1.3. The JPC will determine the JPC operating procedures at its first meeting, including the JPC's policies for replacement of JPC members, and the location of meetings, which will be codified in the written minutes of the first JPC meeting. The Parties may escalate issues to the Executives for input and resolution pursuant to Section 13.1. Each Party's representatives on the Joint Patent Committee will consider comments and suggestions made by the other in good faith. Each Party will bear their own cost of participation on the JPC.

8.2. Filing, Prosecution and Maintenance of Patents.

8.2.1. Patent Filings. Subject to Section 8.2.2(c), the Party responsible for Prosecution and Maintenance of any Patent Rights as set forth in this Section 8.2 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 in such countries as the responsible Party sees fit.

8.2.2. Licensed Patents and Bayer 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 Prosecution and Maintenance of the Isis Core Technology Patents, the Isis Manufacturing and Analytical Patents and the Isis Program Patents.

(b) **Isis Product-Specific Patents and Jointly-Owned Program Patents Covering ISIS-FXI$_{Rx}$.** So long as Bayer has not exercised its right under Section 5.2.1, subject to the obligation to provide information and cooperate, and the step-in rights, under Section 8.2.3 and Section 8.4.3 respectively, Isis will control and be responsible for all aspects of the Prosecution and Maintenance of Isis Product-Specific Patents and Jointly-Owned Program Patents Covering ISIS-FXI$_{Rx}$ using the same level of judgment and diligence (and in the same countries) as Isis uses to Prosecute and Maintain product-specific patents for Isis' own internal drug products. Isis will consider in good faith any comments or instructions Bayer timely provides Isis related to the Prosecution and Maintenance of such Isis Product-Specific Patents and Jointly-Owned Program Patents. Isis will have final decision making authority regarding the Prosecution and Maintenance of such Isis Product-Specific Patents and Jointly-Owned Program Patents. In addition, Isis will Prosecute and Maintain such Isis Product-Specific Patents and Jointly-Owned Program Patents in countries that are in addition to the countries in which Isis Prosecutes and Maintains product-specific patents for Isis' own internal drug products *so long as* (i) Bayer pays the costs of such Prosecution and Maintenance in such additional countries, and (ii) Bayer provides its written request to Isis for such additional countries with a sufficient amount of time in advance of the applicable filing deadline in such countries. Isis may use the legal counsel Isis normally uses to Prosecute and Maintain its other Patent Rights in the relevant country; *provided*, if Isis does not have its own legal counsel in such country Isis will, subject to a conflicts check, use the legal counsel Bayer uses in such country to Prosecute and Maintain Bayer's own Patent Rights in such country.

(c) **Isis Product-Specific Patents and Jointly-Owned Program Patents Covering ISIS-FXI$_{Rx}$-2 or [***]**. Prior to and after the exercise of an Option and so long as Bayer has not exercised its right under Section 5.2.2, subject to the obligation to provide information and cooperate, and the step-in rights, under Section 8.2.3 and Section 8.4.3 respectively, Isis will control and be responsible for all aspects of the Prosecution and Maintenance of all Isis Product-Specific Patents and Jointly-Owned Program Patents that are the subject of such Option using the same level of judgment and diligence (and in the same countries) as Isis uses to Prosecute and Maintain product-specific patents for Isis' own internal drug products. Isis will consider in good faith any comments or instructions Bayer timely provides Isis related to the Prosecution and Maintenance of such Isis Product-Specific Patents and Jointly-Owned Program Patents. Isis will have final decision making authority regarding the Prosecution and Maintenance of such Isis Product-Specific Patents and Jointly-Owned Program Patents. In addition, Isis will Prosecute and Maintain such Isis Product-Specific Patents and Jointly-Owned Program Patents in countries that are in addition to the countries in which Isis Prosecutes and Maintains product-specific patents for Isis' own internal drug products *so long as* (i) Bayer pays the costs of such Prosecution and Maintenance in such additional countries, and (ii) Bayer provides its written request to Isis for such additional countries with a sufficient amount of time in advance of the applicable filing deadline in such countries. Isis may use the legal counsel Isis normally uses to Prosecute and Maintain its other Patent Rights in the relevant country; *provided*, if Isis does not have its own legal counsel in such country Isis will, subject to a conflicts check, use the legal counsel Bayer uses in such country to Prosecute and Maintain Bayer's own Patent Rights in such country.

(d) **Bayer Patents**. Bayer will control and be responsible for all aspects of the Prosecution and Maintenance of all Bayer Patents, subject to Section 8.2.3.

(e) **Isis Product-Specific Patents Arising From Prosecution of Isis Core Technology Patents.** If each Party's patent representatives believe an Isis Core Technology Patent contains claimable subject matter that, if prosecuted under a separate patent application, could become an Isis Product-Specific Patent, then upon Bayer's written request (and at Bayer's expense) Isis will use Commercially Reasonable Efforts to prosecute such Isis Core Technology Patent in a manner that would result in a separate patent application meeting the requirements of an Isis Product-Specific Patent. Once Isis has prosecuted such Isis Core Technology Patent in a manner that results in a separate patent application meeting the requirements of an Isis Product-Specific Patent, Bayer will have the right but not the obligation to request assignment of such separate Isis Product-Specific Patent under Section 5.2; *provided*, *that* Bayer will not have the right to (and Isis will not be required to) prosecute such Patent Right to include claims that are (i) directed to subject matter applicable to ASOs in general, (ii) directed to an ASO, the sequence of which targets an RNA that does not encode an Exclusive Target, or (iii) directed to an RNA that is not an Exclusive Target.

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

(a) Each Party will keep the other Party informed through the Joint Patent Committee (or through the other Party's patent representative if no JPC exists) as to material developments with respect to the filing, Prosecution and Maintenance of the Product-Specific Patents or Jointly-Owned Program Patents for which such Party has responsibility for Prosecution and Maintenance pursuant to Section 8.2.2, or this Section 8.2.3, 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 Bayer elects (i) not to file and prosecute patent applications for the Jointly-Owned Program Patents or Isis Product-Specific Patents that have been assigned to Bayer under this Agreement or the Bayer Product-Specific Patents ("***Bayer-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 Bayer-Prosecuted Patent in a particular country, or (iii) not to file and prosecute patent applications for the Bayer-Prosecuted Patent in a particular country following a written request from Isis to file and prosecute in such country, then Bayer 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 Bayer-Prosecuted Patent in the applicable country at its own expense with counsel of its own choice. In such case, Bayer will cooperate with Isis to file for, or continue to Prosecute and Maintain or enforce, or otherwise pursue such Bayer-Prosecuted Patent in such country in Isis' own name, but only to the extent that Bayer is not required to take any position with respect to such abandoned Bayer-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 Bayer under this Agreement. Notwithstanding anything to the contrary in this Agreement, if Isis assumes responsibility for the Prosecution and Maintenance of any such Bayer-Prosecuted Patent under this Section 8.2.3(b), Isis will have no obligation to notify Bayer if Isis intends to abandon such Bayer-Prosecuted Patent.

(c) If, during the Agreement Term, Isis intends to abandon any Isis Product-Specific Patent or Jointly-Owned Program Patents for which Isis is responsible for Prosecution and Maintenance without first filing a continuation or substitution, then Isis will notify Bayer of such intention at least [***] days before such Patent Right will become abandoned, and Bayer will have the right, but not the obligation, to assume responsibility for the Prosecution and Maintenance thereof at its own expense (subject to Section 8.3.1) with counsel of its own choice. Notwithstanding anything to the contrary in this Agreement, if Bayer assumes responsibility for the Prosecution and Maintenance of any such Isis Product-Specific Patent under this Section 8.2.3(c), Bayer will have no obligation to notify Isis if Bayer intends to abandon such Isis Product-Specific Patent. Section 8.2.3(c) shall not apply for Isis Product-Specific Patents and Jointly-Owned Program Patents Covering ISIS-FXI$_{Rx}$-2 or [***] if the applicable Option Deadline has passed and Bayer has not exercised its Option as provided under Section 2.4. For clarity, if Bayer assumes responsibility for any such Isis Product-Specific Patent under this Section 8.2.3(c), such Isis Product-Specific Patent shall not be taken into account in determining the Full Royalty Period.

(d) The Parties, through the Joint Patent Committee (or the Parties' patent representatives if no JPC exists), will cooperate in good faith to determine if and when any divisional or continuation applications will be filed with respect to any Jointly-Owned Program Patents or Product-Specific Patents, and where a divisional or continuation patent application filing would be practical and reasonable, then such a divisional or continuation filing will be made.

(e) If the Party responsible for Prosecution and Maintenance pursuant to Section 8.2.2 intends to abandon such Jointly-Owned Program Patent without first filing a continuation or substitution, then such Party will notify the other Party of such intention at least [***] days before such Jointly-Owned Program Patent will become abandoned, and such other Party will have the right, but not the obligation, to assume responsibility for the Prosecution and Maintenance thereof at its own expense (subject to Section 8.3.1) with counsel of its own choice, in which case the abandoning Party will, and will cause its Affiliates to, assign to the other Party (or, if such assignment is not possible, grant a fully-paid exclusive license in) all of their rights, title and interest in and to such Jointly-Owned Program Patents. If a Party assumes responsibility for the Prosecution and Maintenance of any such Jointly-Owned Program Patents under this Section 8.2.3(e), such Party will have no obligation to notify the other Party of any intention of such Party to abandon such Jointly-Owned Program Patents.

(f) In addition, the Parties will consult, through the Joint Patent Committee (or the Parties' patent representatives if no JPC exists), 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.

8.3. Patent Costs.

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

8.3.2. Licensed Patents and Bayer Patents. Except as set forth in Section 8.3.1, 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 8.2.

8.4. Defense of Claims Brought by Third Parties; Oppositions.

8.4.1. ISIS-FXI$_{Rx}$-2 [***] – Prior to Option Exercise. 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 ISIS-FXI$_{Rx}$-2 or [***] being researched or Developed under a New Drug Option Program with respect to which Bayer has not yet exercised its Option, 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. Bayer will reasonably assist Isis in defending such Proceeding and cooperate in any such litigation at the request and expense of Isis. Isis will provide Bayer with prompt written notice of the commencement of any such Proceeding that is of the type described in this Section 8.4, and Isis will keep Bayer apprised of the progress of such Proceeding. If Isis elects not to defend against such a Proceeding, then Isis will so notify Bayer in writing within [***] days after Isis first receives written notice of the initiation of such Proceeding, and Bayer will have the right, but not the obligation, to defend against such Proceeding at its sole cost and expense and thereafter Bayer 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 8.4. Each Party will provide the other Party with prompt written notice of the commencement of any such Proceeding under this Section 8.4, 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.

8.4.2. **Products Licensed to Bayer**. 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 Bayer under this Agreement, then Bayer will have the first right, but not the obligation, to defend against any such Proceeding at its sole cost and expense. If Bayer elects to defend against such Proceeding, then Bayer will have the sole right to direct the defense and to elect whether to settle such claim. Isis will reasonably assist Bayer in defending such Proceeding and cooperate in any such litigation at Bayer's request and expense. Bayer will provide Isis with prompt written notice of the commencement of any such Proceeding that is of the type described in this Section 8.4, and Bayer will keep Isis apprised of the progress of such Proceeding. If Bayer elects not to defend against a Proceeding, then Bayer will so notify Isis in writing within [***] days after Bayer first receives written notice of the initiation of such Proceeding, and Isis shall not have the right to defend against such a Proceeding *unless* Isis is a defendant under such Proceeding in which event Isis shall have the right to defend against such a Proceeding at its sole cost and expense. Thereafter, Isis will have the sole right to direct the defense of such Proceeding, including the right to settle such claim (but only with the prior written consent of Bayer, 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 8.4. Each Party will provide the other Party with prompt written notice of the commencement of any such Proceeding under this Section 8.4, 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.

8.4.3. **Interferences, Reissues, Re-Examinations and Oppositions**. If a Third Party initiates a Proceeding related to an interference, reissue, re-examination or opposition of an Isis Product-Specific Patent, Bayer will by written notice to Isis either (i) control the defense of such Proceeding at Bayer's expense, or (ii) have Isis control the defense of such Proceeding at Bayer's expense, *provided* if Bayer makes no such election within a reasonable period of time, then Isis will have the right, but not the obligation, to control the defense of such Proceeding and Isis and Bayer will evenly split the cost of such defense.

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

8.5.1. **Duty to Notify of Competitive Infringement**. If either Party learns of an infringement, unauthorized use, misappropriation or threatened infringement by a Third Party with respect to any Product-Specific Patents by reason of the development, manufacture, use or commercialization of a product directed against the RNA that encodes an Exclusive Target ("***Competitive Infringement***"), such Party will promptly notify the other Party in writing and will provide such other Party with available evidence of such Competitive Infringement; *provided*, *however*, that for cases of Competitive Infringement under Section 8.5.6 below, such written notice will be given within 10 days.

8.5.2. **Control of Competitive Infringement Proceedings**. For any Competitive Infringement with respect to a particular Product for which Bayer is Developing or Commercializing under this Agreement, so long as part of such Proceeding Bayer also enforces any Orange Book Patents Controlled by Bayer being infringed that Cover the Product, then Bayer will have the first right, but not the obligation, to institute, prosecute, and control a Proceeding to enforce the Isis Product-Specific Patents 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*, Bayer will have the right to control such litigation. If Bayer 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 Bayer 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 Bayer will have the right to be represented in any such action by counsel of its own choice at its own expense. Isis will at all times have the sole right to institute, prosecute, and control any Proceeding under this Section 8.5.2 to the extent involving Isis Core Technology Patents or Isis Manufacturing and Analytical Patents.

8.5.3. **Joinder; Cooperation**.

(a) If a Party initiates a Proceeding in accordance with this Section 8.5, the other Party agrees to be joined as a party plaintiff upon request of the first Party and to give the first Party reasonable assistance and authority to file and prosecute the Proceeding. Subject to Section 8.5.4, each Party bears its own cost and expense incurred pursuant to this Section 8.5.3(a).

(b) If one Party initiates a Proceeding in accordance with this Section 8.5.3, 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.

(c) If a Third Party asserts in writing or in any legal proceeding that any of the Licensed Patents are unenforceable based on any term or condition of this Agreement, the Parties will amend this Agreement as may reasonably be required to effect the original intent of the Parties, including preserving the enforceability of such Licensed Patents.

8.5.4. **Share of Recoveries**. Any damages or other monetary awards recovered with respect to a Proceeding brought pursuant to this Section 8.5 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 [***]% to [***]% in favor of the Party initiating the Proceeding pursuant to Section 8.5.

8.5.5. **Settlement**. Notwithstanding anything to the contrary in this ARTICLE 8, neither Party may enter a settlement, consent judgment or other voluntary final disposition of a suit under this ARTICLE 8 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 or admits any fault or liability on the part of the other Party without first obtaining the written consent of the Party that Controls the relevant Patent Right which shall not be unreasonably withheld, delayed or conditioned.

8.5.6. **35 USC 271(e)(2) Infringement**. Notwithstanding anything to the contrary in this Section 8.5, solely with respect to Licensed Patents that have not been assigned to Bayer under this Agreement, for a Competitive Infringement under 35 USC 271(e)(2), the time period set forth in Section 8.5 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.

8.6. **Other Infringement**.

8.6.1. **Jointly-Owned Program Patents**. With respect to the infringement of a Jointly-Owned Program Patent, 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 8.6.1 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 8.6.1, [***]; and (B) if only one Party initiates the Proceeding pursuant to this Section 8.6.1, any damages or other monetary awards will be allocated [***]% to [***]% in favor of the Party initiating the Proceeding pursuant to this Section 8.6.1.

8.6.2. **Patents Solely Owned by Isis**. Unless agreed otherwise between the Parties in this ARTICLE 8, Isis will retain all rights to pursue an infringement of any Patent Right solely owned by Isis and Isis will retain all recoveries with respect thereto.

8.6.3. **Patents Solely Owned by Bayer**. Unless agreed otherwise between the Parties in this ARTICLE 8, Bayer will retain all rights to pursue an infringement of any Patent Right solely owned by Bayer and Bayer will retain all recoveries with respect thereto.

8.7. **Patent Listing**. Bayer will promptly, accurately and completely list, with the applicable Regulatory Authorities during the Agreement Term, all applicable Orange Book Patents. Prior to such listings, the Parties will meet, through the Joint Patent Committee (or between the Parties if no Joint Patent Committee exists), to evaluate and identify all applicable Patent Rights, and Bayer will have the right to review, where reasonable, original records relating to any invention for which Patent Rights are being considered by the Joint Patent Committee (or the Parties) for any such listing. Notwithstanding the preceding sentence, Bayer will retain final decision-making authority as to the listing of all applicable Orange Book Patents for such Product (excluding Isis Core Technology Patents), regardless of which Party owns such Orange Book Patent.

8.8. **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, once agreed to by the other Party, it will notify the other Party 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).

8.9. **Obligations to Third Parties**. Notwithstanding any of the foregoing, each Party's rights and obligations with respect to Licensed Technology under this ARTICLE 8 will be subject to the restrictions set forth in Section 5.1.7, *provided*, *however*, that, to the extent that Isis has a non-transferable right to prosecute, maintain or enforce any Patent Rights licensed to Bayer hereunder and, this Agreement purports to grant any such rights to Bayer, Isis will act in such regard with respect to such Patent Rights at Bayer's direction.

8.10. **Additional Rights and Exceptions**. Notwithstanding any provision of this ARTICLE 8, 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.

8.11. **Patent Term Extension.** The Parties will cooperate with each other in gaining patent term extension for Isis Product-Specific Patents wherever applicable to a Product. After Bayer is granted the applicable license under Section 5.1 with respect to the applicable Isis Product-Specific Patents, Bayer will determine which such relevant Isis Product-Specific Patents will be extended.

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

8.13. **Patent Challenge**. If, during the Agreement Term, with respect to rights to the Licensed Patents that are included in a license granted to Bayer under Section 5.1.1, Section 5.1.2 or Section 5.1.3, Bayer, its Affiliates or Sublicensees, in the United States or any other country:

(a) commence or otherwise voluntarily determine to participate in (other than as may be necessary or reasonably required to assert a cross-claim or a counter-claim or to respond to a court request or order or administrative law request or order) any action or proceeding, challenging or denying the enforceability or validity of any claim within an issued patent or patent application within such Licensed Patents, or

(b) direct, support or actively assist any other Person (other than as may be necessary or reasonably required to assert a cross-claim or a counter-claim or to respond to a court request or order or administrative law request or order) in bringing or prosecuting any action or proceeding challenging or denying the validity of any claim within an issued patent or patent application within such Licensed Patents,

then, [***]. In addition, if Bayer, its Affiliates or Sublicensees take any of the actions described in clause (a) or clause (b) of this Section 8.13 and [***], Bayer will [***].

ARTICLE 9.
REPRESENTATIONS AND WARRANTIES

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

9.1.1. 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;

9.1.2. 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;

9.1.3. 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;

9.1.4. 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; and

9.1.5. all employees, consultants, or (sub)contractors (except academic collaborators or Third Parties under material transfer agreements) of such Party or Affiliates performing development activities hereunder on behalf of such Party 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.

9.2. **Representations and Warranties of Isis**. Isis hereby represents and warrants to Bayer as of the Execution Date and the Effective Date, that:

9.2.1. Isis is the owner of, or otherwise has the right to grant all rights and licenses it purports to grant to Bayer with respect to the Licensed Technology under this Agreement for ISIS-FXI$_{Rx}$ as it exists on the Execution Date and the Effective Date;

9.2.2. all Licensed Patents that are owned by Isis ("***Isis Owned Patents***") have been filed and maintained properly and correctly in all material respects;

9.2.3. 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 9.2.1 not true;

9.2.4. each of the Isis Owned Patents that are Isis Product-Specific 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;

9.2.5. to Isis' Knowledge, each of the Isis Owned Patents that are Isis Core Technology 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;

9.2.6. Isis has not received any written claim alleging that any of the Licensed Technology is invalid or unenforceable, including any Isis Owned Patents required in order for Isis to perform the Isis Completion Activities;

9.2.7. Isis has not received any written claim alleging that any of Isis' activities relating to ISIS-FXI$_{Rx}$ infringes any intellectual property rights of a Third Party;

9.2.8. to Isis' Knowledge, (i) 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 is not aware, of any breach by any party to the Isis In-License Agreements, and (iii) Isis' performance of its obligations under this Agreement (including the Strategic Plan as it exists on the Execution Date) will not constitute a breach of Isis' obligations under the Isis In-License Agreements and the licenses granted to Isis thereunder;

9.2.9. to Isis' Knowledge, in respect of the pending United States patent applications included in the Isis Owned 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;

9.2.10. to Isis' Knowledge, neither Isis nor its Affiliates owns or Controls any Patent Rights or Know How covering formulation or delivery technology as of the Execution Date or the Effective Date that would be necessary in order for Bayer to further Develop or Commercialize ISIS-FXI$_{Rx}$ contemplated under the Strategic Plan as it exists on the Execution Date;

9.2.11. except for the activities Isis is obligated to conduct under the Prior Agreements as in effect on the Execution Date and the Effective Date, Isis does not conduct any activities which would violate ARTICLE 4;

9.2.12. to Isis' Knowledge, Bayer's performance of its rights and obligations under this Agreement does not infringe any of Isis' or Third Party's Patent Rights, Know-How or other intellectual property rights; *provided*, Bayer cannot assert a claim against Isis for breach of this Section 9.2.12 related to any Third Party Patent Rights Bayer has Knowledge of as of the Execution Date or the Effective Date;

9.2.13. all preclinical and clinical studies and trials conducted by Isis on ISIS-FXI$_{Rx}$, have been conducted in accordance with Applicable Law and, as applicable, GLP and GCP, and to Isis' Knowledge no claim for injury, loss or damage has been initiated or received in respect of any such studies or trials; and

9.2.14. to Isis' Knowledge, Isis has not employed or otherwise used in any capacity the services of any person or entity debarred under Section 21 U.S.C. § 335a for purposes of conducting the preclinical and clinical studies and trials on ISIS-FXI$_{Rx.}$

9.3. **DISCLAIMER OF WARRANTY. EXCEPT FOR THE EXPRESS WARRANTIES SET FORTH IN THIS ARTICLE 9, BAYER 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 BAYER 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 10.
INDEMNIFICATION; INSURANCE

10.1. **Indemnification by Bayer**. Bayer agrees to defend Isis, its Affiliates and their respective directors, officers, employees 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 a Bayer employee, consultant, Affiliate, Sublicensee, or (sub)contractor in the performance of the activities Bayer agrees to perform under this Agreement, including, the Manufacture, Development or Commercialization of any Product, or (b) any breach by Bayer of any of its representations, warranties or covenants pursuant to 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 (iii) any breach of Applicable Law by any Isis Indemnitee.

10.2. **Indemnification by Isis**. Isis agrees to defend Bayer, its Affiliates and their respective directors, officers, employees and their respective successors, heirs and assigns (collectively, the "***Bayer Indemnitees***"), and will indemnify and hold harmless the Bayer Indemnitees, from and against any Losses arising out of Third Party Claims brought against any Bayer Indemnitee and resulting from or occurring as a result of: (a) any activities that an Isis employee, consultant, Affiliate, Sublicensee, or (sub)contractor has undertaken in respect of Products either prior to the Effective Date or outside the scope of this Agreement, or in the performance of the activities Isis agreed to perform under this Agreement, including, the Manufacture, Development or Commercialization of any Product or Discontinued Product, or (b) any breach by Isis of any of its representations, warranties or covenants pursuant to this Agreement; *except* in any such case to the extent such Losses result from: (i) the negligence or willful misconduct of any Bayer Indemnitee, (ii) any breach by Bayer of any of its representations, warranties, covenants or obligations pursuant to this Agreement, or (iii) any breach of Applicable Law by any Bayer Indemnitee.

10.3. **Procedure**. If a Person entitled to indemnification under Section 10.1 or Section 10.2 (an "***Indemnitee***") seeks such indemnification, such Indemnitee will inform the indemnifying Party in writing of a Third Party Claim as soon as reasonably practicable after such Indemnitee receives notice of such Third Party Claim; *provided*, *however*, that the failure to so notify the indemnifying Party shall not relieve the indemnifying Party of its obligations hereunder except to the extent such failure shall have actually materially prejudiced the indemnifying Party.

10.3.1. Defense of Third Party Claim.

(a) ***Control of the Defense***.

(i) If (y) both Parties are named as defendants in the Third Party Claim and at least one Party seeks indemnification hereunder, or (z) the Third Party Claim relates to a Product liability claim or a claim for the infringement of Third Party intellectual property by a Product, then, within 30 days after receipt of such notice, the Parties will use good faith efforts to mutually agree on which Party will assume control of the defense of such Third Party Claim. If the Parties cannot agree on which Party will assume such control, then Bayer will assume control of the defense of such Third Party Claim at Bayer's expense. In all cases at the conclusion of the Third Party Claim, each Party will have the right to seek indemnification from the other Party, including the costs to defend such Third Party Claim, any damages awarded against the Parties from such Third Party Claim, or any settlements made in accordance with Section 10.3.2 from such Third Party Claim.

(ii) Unless covered by Section 10.3.1(a)(i) above, if a Party is named as a defendant in the Third Party Claim and seeks indemnification hereunder, then, within thirty (30) days after receipt of such notice, the indemnifying Party may, upon written notice thereof to and prior written approval of the Indemnitee, assume control of the defense of the Third Party Claim. If the Indemnitee does not provide its written approval for the indemnifying Party to assume control of the defense of such Third Party Claim, then the indemnifying Party will be relieved of any obligation under this Agreement to indemnify and defend the Indemnitee for such Third Party Claim, *unless* both Parties agree in good faith after the final and binding decision of the court or other authority ruling upon such defense of the Third Party Claim, that such defense was duly conducted by the Indemnitee. If the indemnifying Party receives written approval from the Indemnitee to assume control of the defense but does not assume such control, then the Indemnitee shall control such defense and, at the conclusion of the Third Party Claim, will be entitled to recover from the other Party its defense costs, any damages awarded against such Indemnitee from such Third Party Claim, or any settlements made in accordance with Section 10.3.2 from such Third Party Claim.

(b) ***Participation and Cooperation***. The Party not controlling any such defense hereunder may participate therein at its own expense. The Party controlling such defense shall keep the other Party advised of the status of such Third Party Claim and the defense thereof and shall consider in good faith reasonable recommendations made by the other Party with respect thereto. The Party not controlling such defense shall, and shall cause each of its Affiliates and each of their respective directors, officers and employees to reasonably cooperate in the defense or prosecution thereof and shall 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 shall include reasonable retention by such Party of records and information that are reasonably relevant to such Third Party Claim, and making such Party, its Affiliates and its and their respective directors, officers and employees available on a mutually convenient basis to provide additional information and explanation of any records or information provided, and the Party controlling the defense of such Third Party Claim shall reimburse the respective other Party for all of its related reasonable out-of-pocket expenses.

10.3.2. **Settlement of Third Party Claim**. No Indemnitee shall agree to any settlement of any such Third Party Claim without the prior written consent of the indemnifying Party, which shall not be unreasonably withheld, delayed or conditioned. The indemnifying Party shall not agree to any settlement of such Third Party Claim or consent to any judgment in respect thereof that does not include a complete and unconditional release of the Indemnitee from all liability with respect thereto or that imposes any liability or obligation on the Indemnitee without the prior written consent of the Indemnitee which shall not be unreasonably withheld, conditioned or delayed.

10.4. Insurance.

10.4.1. Isis' Insurance Obligations. Isis will maintain, at its cost, reasonable insurance against liability and other risks associated with its activities contemplated by this Agreement.

10.4.2. Bayer's Insurance Obligations. Bayer will maintain, at its cost, reasonable insurance against liability and other risks associated with its activities contemplated by this Agreement in accordance with its internal insurance policy consistently applied.

10.5. LIMITATION OF CONSEQUENTIAL DAMAGES. **EXCEPT FOR (a) THIRD PARTY CLAIMS THAT ARE SUBJECT TO INDEMNIFICATION UNDER THIS ARTICLE 10, (b) CLAIMS ARISING OUT OF A PARTY'S WILLFUL MISCONDUCT OR FRAUD UNDER THIS AGREEMENT, (c) A PARTY'S BREACH OF ARTICLE 4, (d) ISIS' BREACH OF EXCLUSIVITY UNDER SECTION 5.1.1 THROUGH SECTION 5.1.3, (e) CLAIMS ARISING OUT OF A PARTY'S BREACH OF ITS CONFIDENTIALITY OBLIGATIONS UNDER THIS AGREEMENT, NEITHER PARTY NOR ANY OF ITS AFFILIATES WILL BE LIABLE TO THE OTHER PARTY TO THIS AGREEMENT OR ITS AFFILIATES FOR ANY INCIDENTAL, CONSEQUENTIAL, SPECIAL, PUNITIVE OR OTHER INDIRECT DAMAGES OR LOST OR IMPUTED PROFITS OR ROYALTIES, LOST DATA OR COST OF PROCUREMENT OF SUBSTITUTE GOODS OR SERVICES, WHETHER LIABILITY IS ASSERTED IN CONTRACT, TORT (INCLUDING NEGLIGENCE AND STRICT PRODUCT LIABILITY), INDEMNITY OR CONTRIBUTION, AND IRRESPECTIVE OF WHETHER THAT PARTY OR ANY REPRESENTATIVE OF THAT PARTY HAS BEEN ADVISED OF, OR OTHERWISE MIGHT HAVE ANTICIPATED THE POSSIBILITY OF, ANY SUCH LOSS OR DAMAGE.**

ARTICLE 11.
TERM; TERMINATION

11.1. Agreement Term; Expiration. This Section 11.1, ARTICLE 12 and ARTICLE 13 of this Agreement shall become effective on the Execution Date and the remainder of the Agreement shall become effective as of the Effective Date and, unless earlier terminated pursuant to the other provisions of this ARTICLE 11, will continue in full force and effect until the expiration of all payment obligations under this Agreement with respect to the last Product (or Discontinued Product) in all countries. The period from the Effective Date until the date of expiration or earlier termination of this Agreement pursuant to this ARTICLE 11 is the "***Agreement Term***". If the antitrust clearance required for ISIS-FXI_{Rx} in accordance with Section 13.6 is not obtained by December 31, 2015 this Agreement, including this Section 11.1, ARTICLE 12 and ARTICLE 13 shall automatically expire.

11.2. Termination of the Agreement.

11.2.1. Bayer's Termination for Convenience. At any time following payment by Bayer of the payment under Section 7.1, subject to Sections 11.3.1, 11.3.2 and 11.3.3 below, Bayer may terminate this Agreement on a Product-by-Product basis for convenience by providing [***] days written notice to Isis of such termination; *provided however*, that for purposes of this ARTICLE 11 ISIS-FXI$_{Rx}$ and ISIS-FXI$_{Rx}$-2 together shall constitute a Product and [***] shall constitute the other Product.

11.2.2. Termination for Material Breach.

(a) Bayer's Right to Terminate for Material Breach. If Isis is in material breach of this Agreement (including with respect to a failure to use Commercially Reasonable Efforts under ARTICLE 1 or ARTICLE 2), then Bayer may deliver notice of such material breach to Isis. If the breach is curable, Isis will have [***] days to cure such breach. If Isis fails to cure such breach within the [***] day period (or during a longer period of time if such breach is not reasonably curable within such [***]-day period, so long as Isis is pursuing a cure in good faith), or if the breach is not subject to cure, Bayer may terminate this Agreement in its entirety if such breach relates to this Agreement in its entirety, or in relevant part as such breach relates to the applicable Product, by providing written notice to Isis.

(b) Isis' Right to Terminate for Material Breach. If Bayer is in material breach of this Agreement (including with respect to a failure to use Commercially Reasonable Efforts under ARTICLE 1 or ARTICLE 2), then Isis may deliver notice of such material breach to Bayer. If the breach is curable, Bayer will have [***] days to cure such breach (except to the extent such breach involves the failure to make a payment when due, which breach must be cured within [***] days following such notice). If Bayer fails to cure such breach within the [***] day (or during a longer period of time if such breach is not reasonably curable within such [***]-day period, so long as Bayer is pursuing a cure in good faith) or [***] 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 as such breach relates to the applicable Product, by providing written notice to Bayer.

11.2.3. Disputes Regarding Material Breach. Notwithstanding the foregoing, if the Breaching Party in Section 11.2.2 disputes the existence, materiality, or failure to cure of any such breach, and provides notice to the Non-Breaching Party of such dispute within such [***]-day or [***]-day period (as applicable), the Non-Breaching Party will not have the right to terminate this Agreement in accordance with Section 11.2.2, unless and until it has been determined in accordance with Section 13.1 that this Agreement was materially breached by the Breaching Party and the Breaching Party fails to cure such breach within [***] days (or during a longer period of time if such breach is not reasonably curable within such [***]-day period, so long as the Non-Breaching Party is pursuing a cure in good faith) 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. In addition, the fact that Bayer is conducting its activities in accordance with the Strategic Plan is not in and of itself dispositive of whether Bayer is or is not using Commercially Reasonable Efforts under this Agreement.

11.2.4. **Termination for Insolvency**. Either Party may terminate this Agreement if, at any time, the other Party files in any court or agency pursuant to any statute or regulation of any state or country a petition in bankruptcy or insolvency or for reorganization or for an arrangement or for the appointment of a receiver or trustee of the Party or of substantially all of its assets; or if the other Party proposes a written agreement of composition or extension of substantially all of its debts; or if the other Party will be served with an involuntary petition against it, filed in any insolvency proceeding, and such petition will not be dismissed within 90 days after the filing thereof; or if the other Party will propose or be a party to any dissolution or liquidation; or if the other Party will make an assignment of substantially all of its assets for the benefit of creditors. Notwithstanding any further rights under Applicable Law, upon written request of the other Party, the Party filing for bankruptcy, insolvency or a similar proceeding as set forth in this Section 11.2.4 shall promptly provide to such other Party all information and documents necessary to prosecute, maintain and enjoy its rights under the terms of this Agreement.

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

11.3.1. **Consequences of Termination of this Agreement**. If this Agreement is terminated by a Party in accordance with this ARTICLE 11 in its entirety or on a Product-by-Product 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., related to a Product or in its entirety):

(a) **Licenses**. Unless otherwise agreed in writing by the Parties, the licenses granted by Isis to Bayer under this Agreement will terminate and Bayer, its Affiliates and Sublicensees will cease selling Products.

(b) **Options**. Bayer's Option will terminate with respect to any terminated New Drug Option Program.

(c) **Exclusivity**. Unless otherwise agreed in writing by the Parties, neither Party will have any further obligations under Section 4.1 of this Agreement.

(d) **Development Candidate Identification Plans**. Neither Party will have any further obligations with respect to the terminated Development Candidate Identification Plan(s).

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

(f) **Return of IND and Documentation**. Bayer will transfer to Isis the IND together with all necessary documentation and information, and will take all necessary actions in relation thereto to affect such transfer.

(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 7 which are achieved before the effective date of termination, accrue as of the date the applicable milestone event is achieved even if the payment is not due at that time. Notwithstanding the foregoing, solely with respect to the Completion of the CS IV Study, if Bayer delivers a notice of termination to Isis under Section 11.2.1 within 45 days after the date Isis delivered the Completion Notice to Bayer regarding Completion of the CS IV Study, then the milestone payment for such milestone event will not be due.

(h) **Survival**. The following provisions of this Agreement will survive the expiration or earlier termination of this Agreement: Section 2.5 (Expiration of New Drug Option Program Term); Section 4.1.2 (Isis-Products); Section 5.1.4(d) (Effect of Termination on Sublicenses); Section 5.1.5 (Consequences of Natural Expiration of this Agreement); Section 5.1.8(b) (Trademark and Domain Names); Section 5.2.4, Section 5.5 (Cross-Licenses Under Program Technology); Section 6.6(c) (The Isis Internal ASO Safety Database), Section 7.14.6 (Records Retention), Section 7.15 (Audits), Section 7.16 (Taxes), Section 8.1.1 (Isis Technology and Bayer Technology), Section 8.1.2 (Agreement Technology), Section 8.12 (Rights in Bankruptcy), Section 11.2.4 (Termination for Insolvency); Section 11.3 (Consequences of Expiration or Termination of this Agreement); ARTICLE 10 (Indemnification; Insurance); ARTICLE 12 (Confidentiality), ARTICLE 13 (Miscellaneous); and APPENDIX 1 (to the extent definitions are embodied in the foregoing listed Articles and Sections).

11.3.2. **Special Consequences of Certain Terminations**. If (A) Bayer terminates this Agreement under Section 11.2.1 (Bayer's Termination for Convenience) or (B) Isis terminates this Agreement under Section 11.2.2(b) (Isis' Right to Terminate for Material Breach) or Section 11.2.4 (Termination for Insolvency), then, in addition to the terms set forth in Section 11.3.1 (Consequences of Termination of this Agreement), the following additional terms will also apply:

(i) Bayer will and hereby does grant to Isis a sublicensable, worldwide, non-exclusive license or sublicense, as the case may be, under all Bayer Technology Controlled by Bayer as of the effective date of such termination that Covers the Discontinued Product solely as necessary to Develop, make, have made, use, sell, offer for sale, have sold, import and otherwise Commercialize the Discontinued Product;

(ii) Bayer will negotiate with Isis in good faith about a sublicensable, worldwide, non-exclusive license or sublicense, as the case may be, under all Bayer Technology Controlled by Bayer as of the effective date of such termination that Covers any [***] used with the Discontinued Product solely as necessary to Develop, make, have made, use, sell, offer for sale, have sold, import and otherwise Commercialize the Discontinued Product. In addition, upon Isis' written request, Bayer will provide Isis with an introduction to any Third Party from which Bayer was sourcing any such [***] used with the Discontinued Product and will not interfere with Isis' or such Third Party's efforts to enter into a license to such a [***] (which will include Bayer releasing such Third Party from any exclusivity Bayer has with such Third Party to the extent necessary for Isis to obtain such a license);

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

(iv) Bayer will transfer to Isis for use with respect to the Development and Commercialization of the Discontinued Product, any Know-How, data, results, regulatory information, filings (including the IND), and files in the possession of Bayer as of the date of such termination or reversion that relate solely to such Discontinued Product, and any other information or material specified in Section 5.4;

(v) Bayer will provide Isis with copies of any internal or external market research reports and other market research documentation if related to Product;

(vi) Bayer will [***] on a non-exclusive, license under any Trademark that is specific to a Discontinued Product solely for use with such Discontinued Product; *provided*, *however*, that in no event will Bayer have any obligation to license to Isis any Trademark used by Bayer in connection with the Product or any other trademarks of Bayer, including any Bayer Marks;

(vii) Isis will control and be responsible for all aspects of the Prosecution and Maintenance of all Jointly-Owned Program Patents, and Bayer will provide Isis with (and will instruct its counsel to provide Isis with) all reasonably required information and records in Bayer's and its counsel's possession related to the Prosecution and Maintenance of such Jointly-Owned Program Patents; and

(viii) upon Isis' written request pursuant to a mutually agreed supply agreement, Bayer will sell to Isis any bulk API and Finished Drug Product in Bayer's possession related to the Discontinued Products that are the subject of the termination at the time of such termination, at a price equal to [***] at the time such material is requested by Isis.

11.3.3. **Termination of Entire Agreement if there is only one Product**. Notwithstanding any provision to the contrary in this ARTICLE 11, if at the time a notice of termination is delivered under this ARTICLE 11 (i) there is only one license in effect under Section 5.1.1, Section 5.1.2 or Section 5.1.3 to a Product, and (ii) Isis is not obligated to conduct any drug discovery activities pursuant to a New Drug Option Programs under ARTICLE 2, then such termination notice will terminate this Agreement in its entirety (including any and all of Bayer's unexercised Options).

ARTICLE 12.
CONFIDENTIALITY

12.1. **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***").

12.2. **Prior Confidentiality Agreement Superseded**. As of the Effective Date, this Agreement supersedes the Amended and Restated Mutual Confidential Disclosure Agreement executed by Isis and Bayer on August 17, 2012 (including any and all amendments thereto). All information exchanged between the Parties under such Confidential Disclosure Agreement will be deemed Confidential Information hereunder and will be subject to the terms of this ARTICLE 12.

12.3. **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, and (ii) to the extent reasonably necessary to file or prosecute patent, copyright and trademark applications (subject to Section 12.4 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) on a need-to-know basis, in communication with actual or potential lenders, investors, consultants, or professional advisors, in each case under confidentiality provisions no less restrictive than those of this Agreement; (iv) to the extent such disclosure is required to comply with existing expressly stated contractual obligations owed to such Party's or its Affiliates' licensor with respect to any intellectual property licensed to the other Party under this Agreement; or (v) as mutually agreed to in writing by the Parties.

12.4. Press Release; Publications; Disclosure of Agreement.

12.4.1. Announcement of Transaction. On or promptly after each of the Execution Date and the Effective Date, the Parties will issue a public announcement of the execution of this Agreement in form and substance mutually agreed by the Parties.

12.4.2. Other Disclosures. Except to the extent required to comply with applicable law, regulation, rule or legal process or as otherwise permitted in accordance with this Section 12.4, neither Party nor such Party's Affiliates will make any public announcements, press releases or other public disclosures concerning a Product, a New Drug Option Program, this Agreement or the terms or the subject matter hereof without the prior written consent of the other, which will not be unreasonably withheld, conditioned or delayed.

12.4.3. Use of Name. Except as set forth in Section 12.4.8, 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.

12.4.4. Notice of Significant Events; Disclosure of Information Related to Products. Each Party will immediately notify (and provide as much advance notice as possible, but at a minimum two Business Days advance notice to) the other Party of any event materially related to a Product (including in such notice any disclosure of the starting, stopping or clinical hold of a Clinical Study, clinical data or results, material regulatory discussions, filings or Approval or Bayer's sales projections related to a Product) so the Parties may analyze the need for or desirability of publicly disclosing or reporting such event. If Bayer intends to make a press release or similar public communication disclosing material information regarding a Product licensed by Bayer hereunder, including starting, stopping or clinical hold of a Clinical Study, clinical data or results, material regulatory discussions, filings, Approval or Bayer's sales projections related to a Product) (i) Bayer will submit such proposed communication to Isis for review at least two Business Days in advance of such proposed public disclosure, (ii) Isis will have the right to review and recommend changes to such communication, and (iii) Bayer will in good faith consider any changes that are timely recommended by Isis.

12.4.5. Scientific or Clinical Presentations. The Parties agree to use Commercially Reasonable Efforts to control public scientific disclosures of results of the Development activities under this Agreement to prevent any potential adverse effect of any premature public disclosure of such results. Each Party will first submit to the other Party an early draft of all such publications or presentations, whether they are to be presented orally or in written form, at least 14 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 under this Agreement. If, during such 14 day period, the other Party informs such Party that its proposed publication contains Confidential Information the Parties shall discuss the matter in good faith and use Commercially Reasonable Efforts to resolve the matter. If at any time during such 14-day period, the other Party informs such Party that its proposed publication discloses inventions made by either Party 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. Nothing in this Section 12.4.5 shall be construed to restrict the right of an academic collaborator to publish clinical trial data in accordance with good publication practices or guidelines.

12.4.6. **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.

12.4.7. **Subsequent Disclosure**. Notwithstanding the foregoing, to the extent information regarding this Agreement or a 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.

12.4.8. **Acknowledgment**. Bayer will acknowledge in any press release, public presentation or publication regarding a Product, Isis' role in discovering and developing the Product, that the Product is under license from Isis and otherwise acknowledge Isis' contributions, and Isis' stock ticker symbol (Nasdaq: ISIS). Isis may include the Product (and identify Bayer as its partner for the Product) in Isis' drug pipeline.

ARTICLE 13.
MISCELLANEOUS

13.1. **Dispute Resolution**.

13.1.1. **General**. The Parties recognize that a dispute may arise relating to this Agreement ("***Dispute***"). Except as set forth in Sections 1.3.2, 7.11.3(c), 8.1.3(b) and 13.1.5, any Dispute between the Parties or its Affiliates will be resolved in accordance with this Section 13.1.

13.1.2. **Continuance of Rights and Obligations during Pendency of Dispute Resolution**. If there are any Disputes in connection with this Agreement, including Disputes related to termination of this Agreement under ARTICLE 11, all rights and obligations of the Parties will continue until such time as any Dispute has been resolved in accordance with the provisions of this Section 13.1.

13.1.3. **Escalation**. Subject to Section 13.1.5, any claim, Dispute, or controversy as to the breach, enforcement, interpretation or validity of this Agreement will be referred to the Head of Development of Bayer Healthcare prior to FDA Approval of a Product and to the Head of the Bayer Pharmaceutical's Business after FDA Approval of a Product and to the Chief Operating Officer of Isis (the "***Executives***") for attempted resolution. If the Executives are unable to resolve such Dispute within 30 days of such Dispute being referred to them, then, upon the written request of either Party to the other Party, the Dispute will be subject to arbitration in accordance with Section 13.1.4, except as expressly set forth in Section 13.1.5 or Section 13.3.

13.1.4. **Arbitration**.

(a) If the Parties fail to resolve the Dispute through Escalation, and a Party desires to pursue resolution of the Dispute, any Dispute shall be finally settled under the Rules of Arbitration of the International Chamber of Commerce by a panel of three arbitrators appointed in accordance with said Rules, *provided however*, that the third arbitrator, who will act as president of the arbitral tribunal, shall not be appointed by the International Court of Arbitration, but by the two arbitrators which have been appointed by either of the Parties in accordance with Article 12 para 4 of said Rules.

(b) The place of arbitration shall be New York, New York and the language to be used in any such proceeding (and for all testimony, evidence and written documentation) shall be English. The IBA Rules on the Taking of Evidence in International Arbitration shall apply on any evidence to be taken up in the arbitration.

(c) Without limiting any other remedies that may be available under law, the arbitrators shall have no authority to award consequential damages not permitted to be recovered pursuant to Section 10.5. The Parties agree to select the arbitrator(s) within 45 days of initiation of the arbitration. The hearing will be concluded within six months after selection of the arbitrator(s) and the award will be rendered within 60 days of the conclusion of the hearing, or of any post hearing briefing, which briefing will be completed by both Parties within 45 days after the conclusion of the hearing. If the Parties cannot agree upon a schedule, then the arbitrator(s) will set the Schedule following the time limits set forth above as closely as practical.

(d) If the arbitration proceedings have been initiated under this Section 13.1.4 in order to fully or partially terminate this Agreement in accordance with Section 11.2.2 for material breach, both Parties shall – during the pendency of the arbitration proceedings – strive to find an amicable solution to resolve the Dispute with the support of the arbitrators. If through such process Isis and Bayer agree to a remediation plan and to a failure remedy that will apply if such breach is not cured (which may include the non-breaching Party's right to terminate this Agreement upon written notice to the breaching Party), then if the breaching Party subsequently materially fails to execute such plan within 90 days after the conclusion of the remediation plan (or during a longer period of time if such breach is not reasonably curable within such 90-day period, so long as the breaching Party is pursuing a cure in good faith) the non-breaching Party will have the right to exercise and receive the applicable failure remedy. In such case the Parties will mutually terminate the pending arbitration procedure and, so long as the non-breaching Party has received the applicable failure remedy, the non-breaching Party shall not be entitled to reinitiate the arbitration proceedings to seek the full or partial termination of this Agreement on the same or essentially the same facts.

(e) EXCEPT IN THE CASE OF COURT ACTIONS PERMITTED BY SECTION 13.1.5 AND FOR CLAIMS NOT SUBJECT TO ARBITRATION PURSUANT TO SECTION 13.1.4 AS SET FORTH IN SECTION 13.1.5, EACH PARTY HERETO WAIVES: (1) ITS RIGHT TO TRIAL OF ANY ISSUE BY JURY, (2) WITH THE EXCEPTION OF RELIEF MANDATED BY STATUTE, ANY CLAIM TO PUNITIVE, EXEMPLARY, MULTIPLIED, INDIRECT, CONSEQUENTIAL OR LOST PROFITS/REVENUES DAMAGES, AND (3) ANY CLAIM FOR ATTORNEY FEES, COSTS AND PREJUDGMENT INTEREST.

(f) Each Party will bear its own attorneys' fees, costs, and disbursements arising out of the arbitration, and will pay an equal share of the fees and costs of the arbitrators; *provided*, *however*, the arbitrators will be authorized to determine whether a Party is the prevailing party, and if so, to award to that prevailing party reimbursement for any or all of its reasonable attorneys' fees, costs and disbursements (including, for example, expert witness fees and expenses, photocopy charges, travel expenses, etc.), and/or the fees and costs of the administrators and the arbitrators.

13.1.5. Injunctive Relief; Court Actions. Notwithstanding anything to the contrary in this Agreement, each Party will be entitled to seek from any court of competent jurisdiction, in addition to any other remedy it may have at law or in equity, injunctive or other equitable relief in the event of an actual or threatened breach of this Agreement by the other Party, without the posting of any bond or other security, and such an action may be filed and maintained notwithstanding any ongoing discussions between the Parties or any ongoing arbitration proceeding. The Parties agree that in the event of a threatened or actual material breach of this Agreement injunctive or equitable relief may be an appropriate remedy. In addition, except as set forth otherwise in Section 7.11.3(c) and Section 8.1.3(b) 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 Patent Rights or other intellectual property rights, and no such claim will be subject to arbitration pursuant to Section 13.1.4.

13.2. **Governing Law; Jurisdiction; Venue; Service of Process**. This Agreement and any Dispute will be governed by and construed and enforced in accordance with the laws of the State of New York, U.S.A., without reference to conflicts of laws principles.

13.3. **Recovery of Losses**. 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 10.1 or Section 10.2, and the offset under Sections 7.11.3(b) and 7.14.2(b)). Except for the offset and credits explicitly set forth in Section 7.15, and Sections 7.11.3(b) and 7.14.2(b), a final and binding decision of the arbitrators in accordance with Section 13.1.4 or by the court of competent jurisdiction in accordance with Section 13.1.5 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.

13.4. **Assignment and Successors**. Neither this Agreement nor any obligation, of a Party hereunder may be assigned by either Party without the consent of the other, which will not be unreasonably withheld, delayed or conditioned, except that each Party may assign this Agreement and the rights, obligations and interests of such Party, in whole or in part, without the other Party's consent, to any of its Affiliates, to any purchaser of all or substantially all of its assets or all or substantially all of its assets to which this Agreement relates or to any successor corporation resulting from any merger, consolidation, share exchange or other similar transaction subject to Section 13.5.1. In addition, Isis may assign or transfer its rights to receive payments under this Agreement (but no liabilities), without Bayer's consent, to an Affiliate or to a Third Party in connection with a payment factoring transaction. Unless explicitly agreed otherwise in writing between the Parties, if any assignment of this Agreement or of any rights or obligations under this Agreement results in [***]. Any purported assignment or transfer made in contravention of this Section 13.4 will be null and void. This Section 13.4 shall apply to the assignment of Licensed Technology *mutatis mutandis*.

13.5. **Change of Control Events**.

13.5.1. **Change of Control Event Involving Bayer**. Bayer will provide written notice to Isis within [***] days following the closing of a Change of Control Event involving Bayer, and such notice will identify the Third Party acquiring company (the "***Bayer-Acquirer***") and the contact information of the person at the Bayer-Acquirer with whom Isis will work to schedule meetings between the Bayer-Acquirer and Isis. Within [***] days following the closing of such Change of Control Event, Bayer will meet with Isis at a mutually agreed date and time at Isis' facilities to discuss any possible impacts of the Change of Control Event for this Agreement.

13.5.2. **Change of Control Event Involving Isis**. Isis will provide written notice to Bayer within [***] days following the closing of a Change of Control Event involving Isis, and such notice will identify the Third Party acquiring company (the "***Isis-Acquirer***") and the contact information of the person at the Isis-Acquirer with whom Bayer will work to schedule meetings between the Isis-Acquirer and Bayer. If a Change of Control Event occurs involving Isis and the Isis-Acquirer that, at the time of the close of such Change of Control Event, is developing in human clinical trials or commercializing an antithrombotic product that competes or may compete with a Product ("***Competing Product***") or, at any time during the Agreement Term after the closing of such Change of Control Event, develops, commercializes or acquires a Competing Product and such Isis-Acquirer has not, within [***] months of either (i) the closing of the Change of Control Event if the Competing Product is being developed in human clinical trials or commercialized as of such closing date or (ii) the date of first development, commercialization or acquisition of such Competing Product (the "***Divestiture Period***") divested itself of the Competing Product, or terminated development and commercialization of such Competing Product, [***].

13.6. **Antitrust Filing**.

13.6.1. 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.

13.6.2. 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 13.6.2 shall 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.

(i) Other than the provisions of Sections 11.1, ARTICLE 12 and ARTICLE 13 which shall apply as of the Execution Date, the rights and obligations of the Parties under this Agreement shall 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 the Agreement shall become effective automatically without the need for further action by the Parties.

13.6.3. 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 13.6.

13.7. **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, 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 permanent or transitory 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.

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

If to Isis, addressed to:	Isis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, CA 92010 Attention: Chief Operating Officer Fax: 760-918-3592
with a copy to:	Isis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, CA 92010 Attention: General Counsel Fax: 760-268-4922
If to Bayer, addressed to:	Bayer Pharma AG Muellerstrasse 178 13353 Berlin Attention: Head of Strategic Marketing General Medicine Fax: +49 30 468 14086
with a copy to:	Bayer Pharma AG Muellerstrasse 178 13353 Berlin Attention: General Counsel Fax: +49 30 468 14086

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

13.9. **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.

13.10. **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.

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

13.12. **Entire Agreement; Modifications**. This Agreement (including the attached Appendices 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.

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

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

13.15. **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 their respective Applicable Law.

13.16. **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.

13.17. **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.

13.18. **Supremacy**. In the event of any express conflict or inconsistency between this Agreement and any Schedule or Appendix hereto, the terms of this Agreement will apply. The Parties understand and agree that the Appendices identifying the Licensed Technology 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.

13.19. **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.

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

13.21. **Debarment**. Neither Party is 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 that 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, which directly or indirectly relate to activities under this Agreement, the other Party will be immediately notified in writing.

13.22. **Remedies at Law**. Without limiting Section 13.3 and except as expressly stated in this Agreement the rights and remedies provided in this Agreement and all other rights and remedies available to either Party at law or in equity are, to the extent permitted by law, cumulative and not exclusive of any other right or remedy now or hereafter available at law or in equity.

[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.

BAYER PHARMA AG

By: */s/ Dieter Weinand*

Name: Dieter Weinand

Title: Chief Executive Officer

By: */s/ Sebastian Guth*

Name: Sebastian Guth

Title: Head of Strategic Marketing General Medicine

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 and Schedules

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APPENDIX 2 – Initial Strategic Plan

APPENDIX 3 – Isis' Development Candidate Checklist and Bayer's Development Candidate Guidelines

APPENDIX 4 – Isis In-License Agreements

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APPENDIX 1

DEFINITIONS

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

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

"***Additional Indication***" means any indication in addition to the First Indication.

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

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

"***Agreement Term***" has the meaning set forth in Section 11.1.

"***Alliance Manager***" has the meaning set forth in Section 3.1.

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

"***API***" means the bulk active pharmaceutical ingredient manufactured in accordance with cGMP (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).

"***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 approval sufficient for the manufacture, distribution, use, marketing and sale of such Product in such jurisdiction in accordance with Applicable Laws.

"***ASO***" means a single-stranded or double-stranded oligonucleotide compound, or analog, variant, mimic, or mimetic thereof, having a sequence that is at least six bases 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.

"***Audit Report***" has the meaning set forth in Section 7.15.

"***Average Regional Price***" has the meaning set forth in Section 7.9.2(b).

"***Average U.S. Price***" has the meaning set forth in Section 7.9.2(b).

"***Bankruptcy Code***" has the meaning set forth in Section 8.12.

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

"***Bayer-Acquirer***" has the meaning set forth in Section 13.5.1.

"***Bayer Base Royalty Rate***" has the meaning set forth in Section 7.9.1.

"***Bayer's Cost of Goods Sold***" has the meaning set forth in Appendix 10.

"***Bayer Excluded Indication***" has the meaning set forth in Section 5.5.1.

"***Bayer Indemnitees***" has the meaning set forth in Section 10.2.

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

"***Bayer Marks***" means any proprietary Bayer name, logotype, Trade Dress (including the name "Bayer" and the "Bayer Cross") other than the Trademark.

"***Bayer Opt-In Technology***" has the meaning set forth in Section 2.2.2.

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

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

"***Bayer Program Know-How***" has the meaning set forth in Section 8.1.2.

"***Bayer Program Patents***" has the meaning set forth in Section 8.1.2.

"***Bayer Program Technology***" has the meaning set forth in Section 8.1.2.

"***Bayer-Prosecuted Patents***" has the meaning set forth in Section 8.2.3(b).

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

"***Bayer Technology***" means the Bayer Program Technology, Bayer's interest in Jointly-Owned Program Technology, Bayer Product-Specific Patents, owned, used, developed by, or licensed to Bayer or its Affiliates that are necessary or useful to Develop, register, Manufacture or Commercialize a Product.

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

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

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

"***Calendar Year***" means a year beginning on January 1 (or, with respect to 2015, the Effective Date) and ending on December 31.

"***Carryover Development Candidate***" has the meaning set forth in Section 2.5.2.

"***Carryover Option***" has the meaning set forth in Section 2.5.2.

"***Carryover Option Deadline***" has the meaning set forth in Section 2.5.2.

"***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 50% 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 50% 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 such Party, taken as a whole, or which results in the holders of the voting equity interests of such Party immediately prior to such merger, consolidation, business combination or similar transaction ceasing to hold 50% 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 Isis, Bayer or their respective Affiliates.

"***Clinical Study***" or "***Clinical Studies***" means, with respect to a Product (or, in the case of Section 4.2 only [***]), a Phase I Clinical Trial, Phase II Clinical Trial, Phase III Clinical Trial or Registration-Directed Trial, Phase IV Clinical Trial or such other study in humans that is conducted in accordance with good clinical practices and is designed to generate data in support or maintenance of an NDA, MAA, JNDA or other similar marketing application.

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

"***Combination Product***" means the combination of the Product and any separately packaged drug or biological product, administered either sequentially or concurrently, whether or not such separately packaged drug or biological product is approved for marketing and sale under Applicable Law.

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

"***Commercially Reasonable Efforts***" means the level of effort, budget and resources normally used by a company in the pharmaceutical industry of similar size as the respective Party or in case there is no such industry standard, the level of effort, budget and resources normally used by the respective Party for a product owned or controlled by it, which is of similar profitability and at a similar stage in its development or product life, taking into account with respect to a product *inter alia* any issues of patent coverage, safety and efficacy, pricing, product profile, the proprietary position of the product, the competitive environment for the product and the likely timing of the product(s) entry into the market, the regulatory environment of the product and other relevant scientific, technical and commercial factors. Commercially Reasonable Efforts shall be determined on a Product-by-Product and country-by-country basis.

"***Competing Product***" has the meaning set forth in Section 13.5.2.

"***Competitive Infringement***" has the meaning set forth in Section 8.5.1.

"***Complete***," "***Completed***," or "***Completion***" means, with respect to a Clinical Study, the point in time at which the primary database lock for such study has occurred and, if such study has a statistical analysis plan, the data generated based on that primary database lock under the statistical analysis plan for such study are available.

"***Completion Notice***" means, with respect to the CS IV Study for ISIS-FXI$_{Rx}$, a written notice containing the tables, listings and figures in a CDISC format to be sent to Bayer within [***] Business Days following database lock in accordance with Isis' standard operating procedures.

"***Compound***" means any ASO that is designed to bind to the RNA that encodes the applicable Exclusive Target, where such ASO is discovered by Isis prior to or in the performance of the applicable Development Candidate Identification Plan.

"***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;

(a) 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;

(b) 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

(c) 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 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 of antisense drugs.

"***Control***" or "***Controlled***" means possession of the ability to grant a license or sublicense hereunder without violating the terms of any agreement with any Third Party; *provided, however*, that if a Party has a right to grant a license or sublicense, with respect to an item of intellectual property to the other Party only upon payment of compensation (including milestones or royalties) to a Third Party ("***Third Party Compensation***") (other than Isis Supported Pass-Through Costs in the case of Isis, and other than Bayer Supported Pass-Through Costs in the case of Bayer), 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 unless the first Party is obliged to pay such costs under this Agreement. 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 owned or controlled by such Third Party immediately prior to the date such Third Party becoming an Affiliate of a Party hereunder will be included in the licenses granted hereunder by virtue of such Third Party becoming an Affiliate of such Party.

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

"***CS IV Study***" means the Phase II Clinical Trial Isis is conducting to assess the pharmacokinetics and pharmacodynamics of ISIS-FXI_{Rx} in patients on dialysis in accordance with the Strategic Plan.

"***Develop***," "***Developing***" or "***Development***" means, with respect to a product containing an ASO (including a Product) after such ASO-product is designated as the development candidate, any and all non-clinical, clinical or regulatory activity with respect to such ASO-product to seek approval by a regulatory authority to market and sell such ASO-product (including the submission of all necessary filings with applicable Regulatory Authorities to support such preclinical and clinical activities and Approval), including pharmacokinetic and toxicology studies required to meet the requirements for filing an IND and filing an IND with any regulatory authority, human clinical trials conducted after Approval of such ASO-product to seek approval by a regulatory authority to market and sell such ASO-product for additional indications.

"***Development Candidate***" means a Compound that Bayer has determined meets Bayer's internal criteria for, and which Bayer selects as ready to start, IND-Enabling Toxicology Studies as provided herein.

"***Development Candidate Identification Plan***" has the meaning set forth in Section 2.2.1.

"***Disclosing Party***" has the meaning set forth in Section 12.1.

"***Discontinued Product***" means a Product for which Bayer was granted a license under Section 5.1, and which Product is the subject of a termination under this Agreement.

"***Dispute***" has the meaning set forth in Section 13.1.1.

"***Divestiture Period***" has the meaning set forth in Section 13.5.2.

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

"***Domain Names***" means any Domain Name identical or similar with the Trademarks under any ccTLD (country code Top Level Domain) and gTLD (generic Top Level Domain) address area.

"***Drug Discovery***" means, with respect to a product containing an ASO (including a Product), a scope of work that includes human clinical lead optimization with the goal of identifying a development candidate.

"***Drug Discovery Request Notice***" has the meaning set forth in Section 2.1.

"***Drug Safety Information Agreement***" has the meaning set forth in Section 1.8.1.

"***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, shall have been received, authorized, permitted or expired.

"***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.

"[***]" has the meaning set forth in [***].

"***Excluded Payments***" means [***].

"***Exclusive Target***" means (i) Factor XI, and (ii) [***] during the period [***] is the subject of a New Drug Option Program and, after the applicable Option exercise, so long as Bayer is Developing and/or Commercializing [***] under this Agreement.

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

"***Executives***" has the meaning set forth in Section 13.1.3.

"***Factor XI***" means the gene coagulation factor XI (NCBI Gene ID: 2160; example identifier NCBI RefSeq NM_000128), or any alternative splice variants, mutants, polymorphisms and fragments thereof.

[***].

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

"***Field***" means any use or form of administration in humans or non-humans of a Product for any indication.

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

"***First Commercial Sale***" means the first sale of a Product by Bayer, its Affiliate or its Sublicensee to a Third Party in a country after Approval of such Product has been obtained in such country, provided that where such a first commercial sale has occurred in a country for which Pricing Approval is necessary for widespread sale, then such sale shall not be deemed a First Commercial Sale until such Pricing Approval has been obtained. For the avoidance of doubt, supply of Product as samples or to patients for compassionate use, named patient use, Clinical Trials or other similar purposes shall not be considered a First Commercial Sale.

"***First Indication***" has the meaning set forth in Section 1.1

"***Formulation Technology***" means technology designed to enhance the stability or delivery of an oligonucleotide where such technology is not an Oligonucleotide Modification. "***Oligonucleotide Modification***" means [***]. Conjugate Technology is an example of an "*Oligonucleotide Modification*," but does not represent "Formulation Technology." Lipid nanoparticle technology is an example of "*Formulation Technology*."

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

"***Full Royalty Period***" has the meaning set forth in Section 7.9.3(a).

"[***]**"** has the meaning set forth in Section 4.2.

"[***]**"** has the meaning set forth in Section 4.2.

"***Generic Country***" means a country in which a Generic Product is sold.

"***Generic Product***" means, with respect to a particular Product, one or more Third Party product(s) (i) having the same active pharmaceutical ingredient as such Product, and (ii) such Third Party product(s) when taken in the aggregate have a market share (measured in number of prescriptions with the numerator of such fractional share being such Third Party product(s) taken in the aggregate, and the denominator being the total of such Third Party product(s) taken in the aggregate plus such Product taken in the aggregate, as provided by IMS or calculated using such other data as mutually agreed by the Parties (such agreement not to be unreasonably withheld, conditioned or delayed)) during the applicable Calendar Quarter in such country of at least [***]%; *provided, however*, [***].

"***Generic Royalty Quotient***" has the meaning set forth in Section 7.9.3(b).

"***Gross Margin***" means [***].

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

"***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.

"***Indemnitee***" has the meaning set forth in Section 10.3.

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

"***Initial Supply***" has the meaning set forth in Section 1.9.2(a)(i).

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

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

"***Isis-Acquirer***" has the meaning set forth in Section 13.5.2.

"***Isis Completion Activities***" has the meaning set forth in Section 1.7.

"***Isis Core Technology Patents***" means any necessary or useful Patent Rights owned, used, developed by, or licensed to Isis or its Affiliates, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term, claiming subject matter generally applicable to ASOs, other than Isis Product-Specific Patents or Isis Manufacturing and Analytical Patents. A list of Isis Core Technology Patents as of the Effective Date is set forth on APPENDIX 5 attached hereto. APPENDIX 5 will be updated during the Agreement Term with any additional Isis Core Technology Patents claiming technology incorporated into a Product.

"***Isis Excluded Indication***" has the meaning set forth in Section 5.5.2.

"***Isis' Fully Absorbed Cost of Good Methodology***" means the costs incurred by Isis as determined using the methodology set forth in APPENDIX 9 fairly applied and as employed on a consistent basis throughout Isis' operations.

"***ISIS-FXI***$_{Rx}$" means the Compound known as ISIS 416858 having the following sequence and chemistry: 5′-A^{Me}CGG^{Me}CATTGGTG^{Me}CA^{Me}CAG^{Me}U^{Me}U^{Me}U- 3′. The underlined residues are 2'-O-(2-methoxyethyl) ribose (2'-MOE nucleosides). The residues are arranged so that there are five 2'-MOE nucleosides at the 5' and 3'-ends of the molecule flanking a gap of ten 2'-deoxynucleosides. All of the cytosine bases are methylated at the 5-position (5-methylcytosine). Each of the 19 internucleoside linkages is a 3'-O to 5'-O phosphorothioate diester. It should be noted that 2'-(2-methoxyethyl)-5-methyluridine (2'-MOE ^{Me}U) nucleosides are sometimes referred to as 2'-(2-methoxyethyl)ribothymidine (2'-MOE T). ISIS-FXI$_{Rx}$ does not include any product containing Conjugate Technology.

"***ISIS-FXI***$_{Rx}$***-2***" has the meaning set forth in Section 2.1.1. ISIS-FXI$_{Rx}$-2 in its finished form is the finished drug product containing the Development Candidate designated under the ISIS-FXI$_{Rx}$-2 Program as an active pharmaceutical ingredient.

"***ISIS-FXI***$_{Rx}$***-2 Program***" has the meaning set forth in Section 2.1.1.

"[***].

"[***].

"***Isis Indemnitees***" has the meaning set forth in Section 10.1.

"***Isis In-License Agreements***" means the agreements listed on APPENDIX 4. If, as a result of Section 2.2.2, where Bayer has elected to use Bayer Opt-In Technology, or as a result of Section 7.11.3(a) where Isis elects to obtain Additional Core IP, amendments to APPENDIX 4 are required and APPENDIX 4 will be updated to include any additional Isis In-License Agreements.

"***Isis Internal ASO Safety Database***" has the meaning set forth in Section 6.6(a).

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

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

"***Isis Manufacturing and Analytical Patents***" means Patent Rights, including Isis' interest in any Jointly-Owned Program Patents, that claim Manufacturing Technology owned, used, developed by, or licensed to Isis or its Affiliates, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term. A list of Isis Manufacturing and Analytical Patents as of the Effective Date is set forth on APPENDIX 6 attached hereto. APPENDIX 6 will be updated during the Agreement Term with any additional Isis Manufacturing and Analytical Patents claiming technology incorporated into a Product. Isis Manufacturing and Analytical Patents do not include the Isis Product-Specific Patents or the Isis Core Technology Patents.

"***Isis Owned Patents***" has the meaning set forth in Section 9.2.2.

"***Isis Product***" has the meaning set forth in Section 4.1.2.

"***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 7 attached hereto. APPENDIX 7 will be updated during the Agreement Term with any additional Isis Product-Specific Patents claiming technology incorporated into a Product.

"***Isis Program Know-How***" has the meaning set forth in Section 8.1.2.

"***Isis Program Patents***" has the meaning set forth in Section 8.1.2.

"***Isis Program Technology***" has the meaning set forth in Section 8.1.2.

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

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

"[***]" has the meaning set forth in [***].

"***Joint Patent Committee***" or "***JPC***" has the meaning set forth in Section 8.1.3(a).

"***Jointly-Owned Program Know-How***" has the meaning set forth in Section 8.1.2.

"***Jointly-Owned Program Patents***" has the meaning set forth in Section 8.1.2.

"***Jointly-Owned Program Technology***" has the meaning set forth in Section 8.1.2.

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

"***Knowledge***" means – with respect to their respective directors, executives and/or employees – a Party's and its Affiliates' good faith, actual understanding of the facts and information as of the Effective Date; *provided that*, with respect to information regarding the status of Patent Rights or other intellectual property rights, "*Knowledge*" means – with respect to their respective directors, executives and/or employees – such Party's or its Affiliate's good faith, actual understanding of the facts and information as of the Effective Date 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 a Compound that is reasonably determined by Isis' Research Management Committee in accordance with Isis' standard procedures for designating development candidates as [***]. The checklist Isis uses as of the Effective Date when reviewing potential development candidates for approval is attached hereto as APPENDIX 3 [***].

"***Lead Candidate Data Package***" means, with respect to a Lead Candidate, [***].

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

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

"***Licensed Technology***" means, on a Product-by-Product basis, any and all Licensed Patents and Licensed Know-How to the extent necessary or useful to Research, Develop, Manufacture, have Manufactured and Commercialize a Product in the Field.

"***Losses***" has the meaning set forth in Section 10.1.

"***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 in any European Union country.

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

"***Major Indication***" means, with respect to ISIS-FXI$_{Rx}$-2, [***].

"***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, for pre-clinical and clinical purposes, of API or a Product in finished form.

"***Manufacturing Technology***" means (i) methods and materials used in the synthesis or analysis of an oligonucleotide regardless of sequence or chemical modification, and (ii) methods of making components of an oligonucleotide.

"***Material Change***" has the meaning set forth in Section 1.3.2.

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

"***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, with respect to any Product sold by Bayer, its Affiliates or Sublicensees to any unaffiliated Third Party, the gross amount invoiced by Bayer, its Affiliates or Sublicensees to such unaffiliated Third Party and calculated using Bayer's internal audited system used to report such sales, less the following items:

(i) [***] percent ([***]%) of gross amount for transportation, freight insurance, distribution, packing and handling,

(ii) sales and excise taxes or customs duties paid by Bayer, its Affiliates or Sublicensees or any other governmental charges imposed upon the sale of a Product and paid by Bayer, its Affiliates or Sublicensees;

(iii) rebates and premiums granted or allowed by Bayer, its Affiliates or Sublicensees in connection with the sale of a Product;

(iv) allowances or credits granted by Bayer, its Affiliates or Sublicensees to customers on account of governmental requirements, rejections, outdating, returns, billing errors or recalls of a Product;

(v) trade, cash and quantity discounts, bonuses or chargebacks granted by Bayer, its Affiliates or Sublicensees in connection with the sale of a Product;

(vi) costs of customer programs such as cost effectiveness or patient assistance studies or programs designed to aid in patient compliance with medication schedules in connection with the sales of Products;

(vii) [***] percent ([***]%) of gross amount for bad debts; and

(viii) any item substantially similar in character and/or substance to the above.

For the purpose of calculating Net Sales, the Parties recognize that customers may include persons in the chain of commerce who enter into agreements with Bayer, its Affiliates or Sublicensees as to price even though title to the Product does not pass directly from Bayer, its Affiliates or Sublicensees to such customers and even though payment for such Product is not made by such customers directly to Bayer, its Affiliates or Sublicensees; and in such cases, chargebacks paid by Bayer, its Affiliates or Sublicensees to or through a Third Party (such as a wholesaler) that are not described in items (iii) or (v) listed above, can be deducted by Bayer, its Affiliates or Sublicensees from gross revenue in order to calculate Net Sales.

In the event that a Product is sold in the form of a Combination Product, Net Sales for such Combination Product will be adjusted by multiplying actual Net Sales of such Combination Product by the fraction A/(A+B) where A is the invoice price of the Product if sold separately and B is the invoice price of any other active ingredient(s) in the Combination Product, if sold separately. If, on a country-by-country basis, the other active ingredient(s) in the Combination Product are not sold separately in that country, Net Sales shall be calculated by multiplying actual Net Sales of such Combination Product by the fraction A/C where A is the invoiced price of the Product if sold separately and C is the invoiced price of the Combination Product. If, on a country-by-country basis, neither the Product nor the other active ingredient(s) of the Combination Product is sold separately in such country, then the value of the active ingredient(s) for the purpose of determining Net Sales shall be determined between the Parties in good faith.

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

"***New Drug Option Program***" has the meaning set forth in Section 2.1.

"***New Drug Option Program Term***" has the meaning set forth in Section 2.3.

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

"***Option***" has the meaning set forth in Section 2.4.

"***Option Deadline***" has the meaning set forth in Section 2.4.

"***Orange Book Patents***" means the Patent Rights that are listed with, and/or are required to be listed with, applicable Regulatory Authorities Covering any Product being Developed by Bayer, its Affiliates or Sublicensees hereunder that Bayer, its Affiliate or Sublicensee intends to, or has begun to, Commercialize, and that have become the subject of an NDA submitted to any applicable Regulatory Authority, such listings to include, without limitation, all so-called "*Orange Book*" listings required under the Hatch-Waxman Act and all so-called "*Patent Register*" listings as required in Canada. For purposes of determining royalties payable under Section 7.9, Orange Book Patents will include any and all foreign equivalent and counterpart Patent Rights to the Patent Rights described above.

"***Party***" or "***Parties***" means Bayer and Isis individually or collectively.

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

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

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

"***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 I Clinical Trial***" means, with respect to a Product, a human clinical trial that is intended to initially evaluate the safety, metabolism and pharmacokinetics of such Product that would otherwise satisfy the requirements of 21 C.F.R. 312.21(a) or an equivalent clinical trial in a country in the Territory other than the United States.

"***Phase II Clinical Trial***" means, with respect to a Product, a human clinical trial for which the primary endpoints include a determination of safety, dose ranges or an indication of efficacy of such Product in patients being studied as described in 21 C.F.R. §312.21(b), or an equivalent clinical trial in a country in the Territory other than the United States, and that is prospectively designed to generate sufficient data (if successful) to commence pivotal clinical trials.

"***Phase III Clinical Trial***" or "***Registration-Directed Trial***" means, with respect to a Product, a human clinical trial (regardless of whether actually designated as "Phase III") that is prospectively designed, along with other Phase III Clinical Trials, to demonstrate statistically whether such Product is safe and effective for use in humans in the indication being investigated as described in 21 C.F.R. §312.21(c), or an equivalent clinical trial in a country in the Territory other than the United States.

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

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

"***Preliminary Royalty Report***" has the meaning set forth in Section 7.14.2(a).

"***Pricing Approval***" means all applicable governmental pricing and reimbursement approvals required from the relevant Regulatory Authority to market and sell, and/or obtain reimbursement for, the Product in a particular country or jurisdiction.

"***Prior Agreements***" means the agreements listed on APPENDIX 8 attached hereto.

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

"***Product***" means, as applicable (i) ISIS-FXI$_{Rx}$, (ii) ISIS-FXI$_{Rx}$-2, and/or (iii) [***].

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

"***Program Patents***" has the meaning set forth in Section 8.1.2.

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

"***Receiving Party***" has the meaning set forth in Section 12.1.

"***Reconciled Royalty Report"*** has the meaning set forth in Section 7.14.2(b).

"***Reduced Royalty Period***" has the meaning set forth in Section 7.9.3(d).

"***Region***" has the meaning set forth in Section 7.9.2.

"***Regional Adjustment***" has the meaning set forth in Section 7.9.2.

"***Regional Royalty Rate***" has the meaning set forth in Section 7.9.2.

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

"***Research***" means, with respect to a product containing an ASO (including a Product), pre-clinical research, including gene function, gene expression, target validation research, and investigating inhibition of a target in therapeutic models, *but specifically excludes* Drug Discovery, Development and Commercialization.

"***Reverse Royalties***" has the meaning set forth in Section 7.10.1.

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

"[*******]" has the meaning set forth in [***].

"***Royalty Quotient***" has the meaning set forth in Section 7.9.3(c).

"***Specific Performance Milestone Events***" has the meaning set forth in Section 1.6.2.

"***Strategic Plan***" has the meaning set forth in Section 1.1. The initial Strategic Plan agreed to by the Parties as of the Effective Date is attached hereto as APPENDIX 2.

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

"[*******]" has the meaning set forth in [***].

"***Territory***" means worldwide.

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

"***Third Party Claims***" has the meaning set forth in Section 10.1.

"***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.

"***Trade Dress***" means any package design of Bayer such as Bayer's wave design.

"***Trademark***" means any trademark owned and controlled by Bayer and used by Bayer in connection with the marketing of the Product.

"***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.

"[*******]" has the meaning set forth in [***].

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

APPENDIX 2

Initial Strategic Plan as of the Execution Date

[***]

APPENDIX 3

Isis' Development Candidate Checklist

[***]

APPENDIX 4

Isis In-License Agreements

(Relevant to the Strategic Plan as of the Effective Date)

[***]

APPENDIX 5

Isis Core Technology Patents

[***]

APPENDIX 6

Isis Manufacturing and Analytical Patents

[***]

APPENDIX 7

Isis Product-Specific Patents

(Relevant to Factor XI)
[***]

(**Relevant to** [*******])

[***]

APPENDIX 8
PRIOR AGREEMENTS

[***]

APPENDIX 9

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

[***]

APPENDIX 10

Bayer's Cost of Goods Soldor Bayer's COGS shall mean:

[***]

SCHEDULE 1.3.2

Expedited Resolution of Strategic Plan Material Changes Disputes

If, within 10 days after first discussing the matter in good faith, the Parties cannot mutually agree on any Material Change (or whether a proposed change constitutes a Material Change) to the Strategic Plan, the Parties will, as promptly as possible (but no later than 45 days thereafter), convene a meeting of a group of subject matter experts (the "***Group of Experts***") to discuss the matter.

At such meeting each Party will have the right to present its position to the Group of Experts regarding the proposed Material Change. The meeting will be held in person or telephonically as mutually agreed by the Parties and will allow for sufficient time to allow the Parties to each present their views regarding the dispute and for the Group of Experts to express their views on the proposed Material Change. The Group of Experts may comprise, at its core, any standing advisory group Bayer has in place to advise on the Strategic Plan, and each Party will have the unilateral right to choose at least one expert to attend the meeting. Each Party will bear its own costs relating to the meeting.

At the end of such meeting, after considering the Strategic Plan and the value of making the proposed Material Change, with both Parties and the Group of Experts participating in appropriate presentations and discussions, each member of the Group of Experts will provide his or her recommendation regarding the value of making the proposed Material Change.

If, following the meeting of the Group of Experts, the Parties still disagree, then within 15 days thereafter, the Executives will meet in person or telephonically at a date, time and location as mutually agreed. At such meeting, the Executives will use their good faith efforts to mutually agree on a resolution acceptable to both Parties. If, after discussing in good faith, such Executives cannot reach an amicable agreement within two Business Days following the end of such meeting, then Bayer will have the final decision making authority regarding such Material Change, *provided however*, that a Material Change regarding a change of the First Indication shall require the prior written approval of Isis which shall not be unreasonably withheld, conditioned, or delayed.

SCHEDULE 1.6.2

Bayer's Development and Commercialization Activities

[***]

SCHEDULE 1.7

Isis Completion Activities

[***]

SCHEDULE 1.9.2(a)

Terms for Supply of API, Finished Drug Product and Packaged Clinical Study Materials

[***]

SCHEDULE 3.1

Alliance Management Activities

If the Parties mutually agree to appoint Alliance Managers, each Alliance Manager is responsible for:

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

(b) Developing a mutually agreed alliance launch plan covering any major activities and systems that the Parties need to implement within the first 100 days after the Effective Date to support the Strategic Plan;

(c) Organizing each meeting of the Parties, including agendas, drafting minutes, and publishing final minutes;

(d) Preparing status and progress reports on the above as determined necessary by the Parties;

(e) Ensuring compliance in maintaining the Isis Internal ASO Safety Database as outlined in Section 6.6; and

(f) Ensuring proper approval of publications prior to submission as required in Section 12.4.

SCHEDULE 7.9.3(E)

Royalty Calculation Examples

[***]

Exhibit 10.2

LINE OF CREDIT AGREEMENT

by and between

ISIS PHARMACEUTICALS, INC.

as Borrower

and

MORGAN STANLEY PRIVATE BANK, NATIONAL ASSOCIATION

as Lender

TABLE OF CONTENTS

LIST OF SCHEDULES

LIST OF EXHIBITS

BASIC TERMS

Note:	See Schedule I hereto for certain definitions of terms used in these Basic Terms.
Line of Credit Commitment:	A maximum amount of $20,000,000.00, subject to adjustment as set forth under the definition of "Commitment" on Schedule I hereto.
Use of Proceeds:	The proceeds of the Advances shall be available (and the Borrower agrees that the Borrower shall use such proceeds or cause such proceeds to be used) solely to provide for general working capital non-purpose uses. No proceeds of any Advance will be used (i) to purchase or carry any margin stock (as defined in Regulation U) or other securities or to extend credit to others for the purpose of purchasing or carrying margin stock or other securities, (ii) to repay any loan that was used to purchase or carry margin stock or other securities, or (iii) to repay a loan made by an Affiliate of the Lender.
Payments:	All payments to the Lender hereunder shall be made by (i) wire transfer to an account specified by the Lender or (ii) check or money order mailed to Morgan Stanley Private Bank, National Association, P.O. Box 60520, City of Industry, California 91716-0520, or to such other address as may be designated by the Lender from time to time in a written notice to the Borrower. In addition, the Borrower may authorize the Lender to initiate ACH debit entries ("Automatic ACH Payment") to pay amounts due hereunder from an account to be specified by the Borrower in writing in accordance with requirements established by the Lender. After the Lender receives such authorization from the Borrower in the form determined by the Lender, the authorization shall remain in effect until the Lender receives from the Borrower written notice that such authorization is terminated, and both the Lender and the depository institution holding the account debited by the ACH have sufficient time to act on such notice.
Repayment:	The Borrower shall pay to the Lender interest on the unpaid principal amount of the Revolving Loan monthly in arrears not later than (i) if paid by ACH, the tenth (10th) day of each month and (ii) if paid by check, money order or wire transfer, the fifteenth (15th) day of each month (in each case, except for interest on LIBO Rate Loans and SWAP Rate Loans, which shall be paid as set forth below), and, in each case, on the Termination Date and on such other date when the Revolving Loan shall be paid in full pursuant to this Agreement and the other Loan Documents. The Borrower shall pay to the Lender interest on the unpaid principal amount of the Revolving Loan monthly in arrears (i) every thirtieth (30th) day after the commencement of any Interest Period (provided, however, to the extent that the thirtieth (30th) day after the commencement of such Interest Period, or any thirtieth (30th) day thereafter, is not a Business Day, the Borrower shall pay to the Lender interest in accordance with this Section on the first Business Day preceding such thirtieth (30th) day on which interest would otherwise be due) and upon the expiration of the Interest Period for any Revolving Loan that is a LIBO Rate Loan or a SWAP Rate Loan and (ii) on the Termination Date. The Borrower shall pay any outstanding fees, costs, expenses and interest on the unpaid principal amount of the Revolving Loan on the date on which the Revolving Loan shall be paid in full pursuant to this Agreement and the other Loan Documents. The Borrower shall repay to the Lender on the Termination Date the principal amount of the Revolving Loan then outstanding, together with all fees, costs and expenses and accrued and unpaid interest thereon.

Advances:	Advances hereunder may be made by wire transfer pursuant to written wire instructions provided by the Borrower to the Lender. Alternatively, Advances hereunder may be made via ACH deposit to the Designated Account per instructions provided to the Lender by the Borrower. Subject to the provisions of Sections 2.02, 3.01 and 3.02 hereof, the Lender shall endeavor to fund requests for Advances received by 1:00 p.m. (Eastern Time) on any Business Day on the same day the request is received (unless the Borrower requests that any such Advance be made as one or more LIBO Rate Loans or SWAP Rate Loans, in which case the provisions of the section below entitled "Fixed LIBO Rate" or "Fixed SWAP Rate", as applicable, shall apply).
Interest:	The Revolving Loan, other than any LIBO Rate Loan or SWAP Rate Loan, shall bear interest at a floating rate of interest equal to the Monthly LIBO Rate in effect from time to time plus 1.25% (the "Margin") per annum, such rate to change when and as the Monthly LIBO Rate changes, payable in arrears monthly in accordance with the Repayment section of these Basic Terms. If for any reason the Monthly LIBO Rate shall cease to be available, interest shall accrue at a rate per annum equal to the Prime Rate plus the Margin.
Fixed LIBO Rate:	The Borrower shall have the right on prior written notice to the Lender to request that (a) an Advance be made as one or more LIBO Rate Loans or (b) all or a portion of the then outstanding Revolving Loan be converted to one or more LIBO Rate Loans, which request must be received by the Lender by 12:00 noon (Eastern Time) at least two (2) Business Days' prior to any such Advance being made as a LIBO Rate Loan or any conversion of the Revolving Loan to one or more LIBO Rate Loans, and any such Advance or conversion shall be made in accordance with the terms and procedures provided in this section and shall be in an amount not less than the minimum amount specified in Section 2.02(a)(ii) hereof, in which case the applicable interest rate for the Interest Period selected by the Borrower shall be a per annum rate equal to the LIBO Rate determined by the Lender at approximately 12:00 noon (Eastern Time) two (2) Business Days prior to the commencement of such Interest Period plus the Margin (the "Fixed LIBO Rate") and not the floating rate described above. The Borrower shall select the requested duration of the applicable Interest Period (which shall be one (1), two (2), three (3), four (4), six (6), or twelve (12) months) by notifying the Lender in writing at least two (2) Business Days before the date of the requested advance or conversion. The Fixed LIBO Rate shall be in effect for the duration of the Interest Period. Upon the Borrower's request made in accordance with the terms set forth in this section, the requested Advance or Revolving Loan (or portion thereof) will be made or will convert to a LIBO Rate Loan, provided that no Default or Event of Default has occurred or is then continuing. The Borrower will not have any right to change the interest rate on any LIBO Rate Loan until the expiration of the applicable Interest Period and such LIBO Rate Loan shall continue to bear interest at the applicable Fixed LIBO Rate until the end of such Interest Period. Prior to the expiration of any Interest Period, the Borrower may request that a new Interest Period be applied to the applicable LIBO Rate Loan pursuant to the terms and conditions set forth in this section. If the Borrower fails to request a new Interest Period, the LIBO Rate Loan will revert to a Revolving Loan bearing interest at a per annum rate equal to the Monthly LIBO Rate plus the Margin as described above in the paragraph entitled "Interest" upon the expiration of the Interest Period. Notwithstanding the foregoing, the Borrower shall only be permitted to have a maximum of five (5) LIBO Rate Loans and/or SWAP Rate Loans (in the aggregate) outstanding at any given time.

Fixed SWAP Rate:	The Borrower shall have the right on prior written notice to the Lender to request that (a) an Advance be made as one or more Swap Rate Loans or (b) all or a portion of the then outstanding Revolving Loan be converted to one or more SWAP Rate Loans, which request must be received by the Lender by 12:00 noon (Eastern Time) at least two (2) Business Days' prior to any such Advance being made as a SWAP Rate Loan or any conversion of the Revolving Loan to one or more SWAP Rate Loans, and any such Advance or conversion shall be made in accordance with the terms and procedures provided in this section and shall be in an amount not less than the minimum amount specified in Section 2.02(a)(ii) hereof, in which case the applicable interest rate for the Interest Period selected by the Borrower shall be a per annum rate equal to the SWAP Rate determined by the Lender at approximately 12:00 noon (Eastern Time) two (2) Business Days prior to the commencement of such Interest Period plus the Margin (the "Fixed SWAP Rate") and not the floating rate described above. The Borrower shall select the requested duration of the applicable Interest Period (which may extend from the date of the Advance or conversion through the Termination Date) by notifying the Lender in writing at least two (2) Business Days before the date of the requested advance or conversion. The applicable Fixed SWAP Rate shall be in effect for the duration of the Interest Period. Upon the Borrower's request made in accordance with the terms set forth in this section, the requested Advance or Revolving Loan (or portion thereof) will be made or will convert to a SWAP Rate Loan provided that no Default or Event of Default has occurred or is then continuing. The Borrower will not have any right to change the interest rate on any SWAP Rate Loan until the expiration of the applicable Interest Period and such SWAP Rate Loan shall continue to bear interest at the applicable Fixed SWAP Rate until the end of such Interest Period. Prior to the expiration of any Interest Period, the Borrower may request that a new Interest Period be applied to the applicable SWAP Rate Loan pursuant to the terms and conditions set forth in this section. If the Borrower fails to request a new Interest Period, the SWAP Rate Loan will revert to a Revolving Loan bearing interest at a per annum rate equal to the Monthly LIBO Rate plus the Margin as described above in the paragraph entitled "Interest" upon the expiration of the Interest Period. Notwithstanding anything in the foregoing to the contrary, the Borrower shall only be entitled to elect a SWAP Rate Loan with an Interest Period of five (5) years on the Effective Date.
Optional and Mandatory Prepayments:	If at any time the aggregate unpaid principal amount of the Revolving Loan exceeds the Commitment, the Borrower shall immediately make a payment in an amount sufficient to reduce such aggregate unpaid principal amount to an amount that is not greater than the Commitment, provided that such prepayment shall be in addition to, not in lieu of, the provisions of the "Collateral Maintenance" section in these Basic Terms. Upon such prepayment by the Borrower, the Lender shall advise the Borrower of, and the Borrower shall immediately pay to the Lender, accrued and unpaid interest at the interest rate set forth herein on the amount of such prepayment of the Revolving Loan to the date of such prepayment. Each prepayment made hereunder shall be applied by the Lender to repayment of the Revolving Loan in such order as the Lender in its sole and absolute discretion shall select. The Borrower may prepay all or any part of the Revolving Loan (other than any LIBO Rate Loan or SWAP Rate Loan) upon at least two (2) Business Days' prior written notice to the Lender, stating the proposed date and principal amount of such prepayment, without premium or penalty, together with accrued interest to the date of such prepayment on the principal amount prepaid. The Borrower may prepay any LIBO Rate Loan or SWAP Rate Loan upon at least five (5) Business Days' prior written notice to the Lender, stating the proposed date and principal amount of the prepayment. If the notice is given, the Borrower shall prepay such outstanding principal amount of such LIBO Rate Loan or SWAP Rate Loan, together with (a) a Prepayment Premium on the principal amount prepaid and (b) accrued interest to the date of such prepayment on the principal amount prepaid. All calculations and determinations by the Lender of the amount of the Prepayment Premium, if made in accordance with its then standard procedures for so calculating or determining such amount, shall be conclusive absent manifest arithmetic error.

Each prepayment of the Revolving Loan (other than any LIBO Rate Loan or SWAP Rate Loan) made hereunder shall be in a minimum principal amount of $100,000.00 and an integral multiple of $100,000.00 in excess thereof.

Each prepayment of LIBO Rate Loans or SWAP Rate Loans made hereunder shall be in a minimum principal amount of $500,000.00 and an integral multiple of $100,000.00 in excess thereof.

If any prepayment is received by the Lender after 1:00 p.m. (Eastern Time) or on any day other than a Business Day, such prepayment shall be deemed to have been made on the next succeeding Business Day.

Collateral Maintenance: With respect to Collateral held in the Securities Account, if at any time the aggregate unpaid principal amount of the Revolving Loan equals or exceeds the sum of the amounts determined by multiplying the aggregate Market Value of each type of Collateral set forth in Column A of Exhibit A hereto times the corresponding percentage specified in Column C of Exhibit A hereto (a "Curable Shortfall"), then the Borrower shall, within five (5) Business Days, (i) make a payment, (ii) deposit additional Collateral of a type and nature acceptable to the Lender, in its sole and absolute discretion, into the Securities Account, or (iii) make a combination of the payments and deposits specified in clauses (i) and (ii) above, in an amount sufficient to ensure that the aggregate unpaid principal amount of the Revolving Loan is equal to or less than the sum of the amounts determined by multiplying the aggregate Market Value of each type of Collateral set forth in Column A of Exhibit A hereto times the corresponding percentage specified in Column B of Exhibit A hereto (the "Shortfall Cure Amount"). If the Borrower fails to make such payment and/or deposit in respect of the Shortfall Cure Amount within such five (5) Business Day period, the Lender shall have the immediate right, without notice or other action (notwithstanding any prior notice that may have been given in respect of such Curable Shortfall or anything else contained herein), to exercise any or all other remedies available to the Lender herein or under any other Loan Document (including, without limitation, the liquidation of the Collateral held in the Securities Account).

If the Borrower makes a payment to eliminate the Curable Shortfall, the Lender shall apply such payment to reduce the aggregate unpaid principal amount outstanding under the Revolving Loan.

Notwithstanding the foregoing, if at any time the aggregate unpaid principal amount of the Revolving Loan equals or exceeds the sum of the amounts determined by multiplying the aggregate Market Value of each type of Collateral set forth in Column A of Exhibit A hereto times the corresponding percentage specified in Column D of Exhibit A hereto (a "Default Shortfall"; and together with a Curable Shortfall, collectively, a "Shortfall"), then the Borrower must immediately (x) make a payment, (y) deposit additional Collateral of a type and nature acceptable to the Lender, in its sole and absolute discretion, into the Securities Account, or (z) make a combination of the payments and deposits specified in clauses (x) and (y) above, in an amount sufficient to ensure that the aggregate unpaid principal amount of the Revolving Loan is equal to or less than the sum of the amounts determined by multiplying the aggregate Market Value of each type of Collateral set forth in Column A of Exhibit A hereto times the corresponding percentage specified in Column B of Exhibit A hereto (the "Default Shortfall Cure Amount"). If the Borrower fails to immediately make such payment and/or deposit in respect of the Default Shortfall Cure Amount, the Lender shall have the immediate right, without notice or other action (notwithstanding any prior notice given under the preceding paragraph or anything else contained herein), to exercise any or all other remedies available to the Lender herein or under any other Loan Document (including, without limitation, the liquidation of the Collateral held in the Securities Account).

	Only Collateral in the Securities Account of the specific types indicated in Column A of Exhibit A hereto, and having a per share value equal to or greater than that indicated in Column A of Exhibit A hereto for such type of Collateral, if any, shall be included by the Lender in determining the value of the Collateral in the Securities Account for purposes of ascertaining the amount of the Commitment hereunder from time to time or at any time. Additionally, if, at any time more than 25% of the aggregate value of the Collateral in the Securities Account consists of securities issued by a single issuer of the type specified in row (8) of Exhibit A hereto, all of such securities shall be excluded in ascertaining the amount of the Commitment, or in ascertaining the existence of any Shortfall Cure Amount or Default Shortfall Cure Amount, at such time.
Payments and Computations:	The Borrower shall make each payment hereunder in respect of interest on, principal of, or other amount related to the Revolving Loan not later than 12:00 noon (Eastern Time) on the day when due in United States Dollars in same day funds, with payments being so received by the Lender after such time being deemed to have been made on the next succeeding Business Day. All computations of interest hereunder shall be made by the Lender on the basis of a year of three hundred sixty (360) days for the actual number of days (including the first day but excluding the last day) occurring in the period for which such interest is payable. Each determination by the Lender of an interest rate hereunder shall be conclusive and binding for all purposes, absent manifest error. Whenever any payment hereunder shall be stated to be due on a day other than a Business Day, such payment shall be made on the next succeeding Business Day, and such extension of time shall in such case be included in the computation of payment of interest.
Late Charge:	If the Borrower fails to pay any interest or principal payment on the Revolving Loan: (i) in the case of payments made by ACH debit, within ten (10) days after the same becomes due and payable hereunder, the Borrower shall, at the option of the Lender, pay to the Lender a late charge equal to five percent (5%) of the amount of such payment, payable on the eleventh (11th) day after such payment becomes due and payable hereunder; or (ii) in the case of payments made by check, wire transfer or money order, within five (5) days after the same becomes due and payable hereunder, the Borrower shall, at the option of the Lender, pay to the Lender a late charge equal to five percent (5%) of the amount of such payment, payable on the sixth (6th) day after such payment becomes due and payable hereunder.
Default Rate:	In addition to any applicable late charge, upon the occurrence and during the continuance of an Event of Default, the interest on the aggregate unpaid principal amount of the Revolving Loan shall be increased, at the option of the Lender, to a rate equal to the lesser of three percent (3%) per annum above the rate of interest applicable hereunder or the Maximum Rate (the “Default Rate”).
Commitment Fee:	Commitment fee waived.
Other Fees:	The Borrower has paid any fees that are outlined in the Letter of Interest.

Unused Availability Fee:	The Borrower will pay to the Lender an unused availability fee equal to 0.25% per annum of the daily unused portion of the Commitment, which fee shall be payable quarterly, in arrears; provided, however, that such fee shall be waived for this first year of this Revolving Facility.
Notices, Etc.:	All notices and other communications provided for hereunder shall be in writing (including fax communication and any other method of communication authorized by the Lender) and faxed or sent by a reputable overnight courier or delivery service to the Borrower, at the Borrower's address at 2855 Gazelle Ct., Carlsbad, CA 92010 or fax number (760) 268-4922, Attention: Steve Smith (with copy to General Counsel fax (760) 268-4922); or if to the Lender, at its address at Morgan Stanley Private Bank, National Association, c/o Morgan Stanley Smith Barney LLC, 2000 Westchester Avenue, Floor 2NE, Purchase, New York 10577, or fax number (914) 225-9110; or, as to the Borrower or the Lender at such other address or fax number as shall be designated by such party in a written notice to the other party or, in the case of a change of the Borrower's address or fax number, as may be requested by the Borrower by telephonic notice and confirmed in writing by the Lender. All such notices and communications shall, when faxed, be effective upon the faxing thereof or, when sent by reputable overnight courier or delivery system, be effective on the Business Day following the day when the same is sent in such manner, except that notices and communications to the Lender pursuant to Article II shall not be effective until received by the Lender. Delivery by facsimile or other electronic means of an executed counterpart of any amendment or waiver of any provision of this Agreement or of any schedule or exhibit hereto to be executed and delivered hereunder shall be as effective as delivery of an original executed counterpart thereof.

The foregoing Basic Terms are incorporated into and made a part of this Agreement.

LINE OF CREDIT AGREEMENT

LINE OF CREDIT AGREEMENT (this "Agreement"), dated as of June 16, 2015, between ISIS PHARMACEUTICALS, INC. (the "Borrower"), and MORGAN STANLEY PRIVATE BANK, NATIONAL ASSOCIATION, a national banking association (the "Lender").

PRELIMINARY STATEMENTS:

A. The Borrower has requested that the Lender extend to the Borrower a line of credit for the benefit of the Borrower to be used solely to provide for general working capital non-purpose uses.

B. The Lender has agreed to extend such commercial line of credit to the Borrower on the terms and conditions hereinafter set forth.

NOW, THEREFORE, based on the foregoing premises and in consideration of the mutual covenants and agreements contained herein, the parties hereto hereby agree as follows:

ARTICLE I

DEFINITIONS, BASIC LOAN AND ACCOUNTING TERMS

Section 1.01 Certain Defined Terms. In addition to the terms defined elsewhere in this Agreement, the terms used herein shall have the meanings given thereto in the Basic Terms (as defined below) and in Schedule I annexed hereto and incorporated by reference herein.

Section 1.02 Basic Terms, Schedules and Exhibits. The Basic Terms above (the "Basic Terms") and all exhibits and schedules referred to herein are incorporated herein by reference as though set forth herein in full.

Section 1.03 Accounting Terms. All accounting terms not specifically defined herein shall be construed in accordance with GAAP.

ARTICLE II

REVOLVING FACILITY

Section 2.01 The Revolving Facility. The Lender agrees, on the terms and conditions set forth in this Agreement, and in particular Section 2.02 and Section 2.03 hereof, to make Advances to the Borrower from time to time on any Business Day during the period from the Effective Date until the Termination Date, in an aggregate amount of Advances (including LIBO Rate Loans and SWAP Rate Loans) outstanding not to exceed at any time the Commitment. Within the limits of the Commitment, the Borrower may borrow, repay and re-borrow Advances (including LIBO Rate Loans and SWAP Rate Loans). The Borrower shall execute and deliver to the Lender a Line of Credit Promissory Note in form and substance satisfactory to the Lender in the maximum amount of the Commitment (the "Note"). The Note shall evidence the Borrower's unconditional obligation to repay the Lender for all Advances made under this Agreement, together with interest as provided herein. Each Advance under the Commitment shall be deemed evidenced by the Note, which is deemed by this reference to be incorporated herein and made a part hereof.

Section 2.02 Making the Advances. Upon fulfillment of the conditions set forth in Article III hereof, an Advance under this Agreement may be made by the Lender to the Borrower as follows:

(a) The Lender or its Affiliates shall make an Advance by wire transfer or such other means agreed to by the Lender in its sole and absolute discretion as follows:

(i) Wire transfers shall be made pursuant to written notice and wire instructions provided by the Borrower to the Lender not later than (A) 1:00 p.m. (Eastern Time) on the date the Borrower desires such proposed Advance to be funded for Advances other than LIBO Rate Loans and SWAP Rate Loans, or (B) by 12:00 noon (Eastern Time) two (2) Business Days prior to the date of the proposed Advance for LIBO Rate Loans and SWAP Rate Loans. Each such notice of an Advance shall be by telephone, confirmed immediately in writing, or fax or other method then authorized by the Lender, and shall specify therein (A) the requested date of such Advance, (B) the requested amount of such Advance, and (C) any other instructions which are required to enable the Lender to make the Advance. The Lender or its Affiliates shall, on the requested date, cause the proceeds of such Advance to be advanced for or on account of the Borrower by wire transfer to an account designated by, and pursuant to wire instructions provided by, the Borrower or in any other manner agreed to by the Lender.

(ii) Each Advance shall be in an amount greater than or equal to $100,000.00.

(b) The Borrower may request that an Advance be disbursed by wire transfer or such other means as offered by the Lender from time to time. For disbursements requested to be made by wire transfer, the Borrower's request shall specify the deposit account to which proceeds of the Advance are to be sent or deposited. The Lender may rely on account information provided by the Borrower in a wire transfer or other request without investigation and the Borrower bears the entire risk of wire or other transfers to the wrong account because of incorrect account information provided by the Borrower.

(c) If any accrued interest on the Revolving Loan, or any fee or other amount (other than principal on any Advance) payable hereunder shall not be paid by or on behalf of the Borrower as contemplated by the paragraph entitled "Payments and Computations" set forth in the Basic Terms section of this Agreement when such interest, fee or other amount becomes due and payable, the Borrower shall be deemed to have requested the Lender make, and shall be deemed to have agreed to, an Advance hereunder on the due date of, and in the amount of, such interest, fee or other amount. Upon fulfillment of the applicable conditions set forth in Article III, the Lender may, in its sole discretion on such date, make available to the Borrower, the amount of such Advance and cause the proceeds of such Advance to be applied to the payment of such interest, fee or other amount. If, however, on such date the aggregate outstanding principal amount of the Revolving Loan shall be $250,000.00 or less, the Borrower may, on or before (i) the fifteenth (15th) day of each month for payments made via check/lockbox or wire transfer, or (ii) the tenth (10th) day of each month for payments made via ACH next following such date, notify the Lender that the Borrower does not so request or agree to such Advance made pursuant to this clause (c) and that the Borrower has paid or will pay such interest, fee or other amount by other means. If the Borrower shall so notify the Lender, such Advance and such application of proceeds pursuant to this clause (c) shall be cancelled and the Lender shall be deemed not to have so made such Advance or applied the proceeds thereof (and, for purposes of this Agreement, such Advance shall not be outstanding). If, however, the Borrower shall not so notify the Lender on or before (i) the fifteenth (15th) day of each month for payments made via check/lockbox or wire transfer, or (ii) the tenth (10th) day of each month for payments made via ACH next following such date, the Borrower shall be deemed to have confirmed its agreement to such Advance.

Section 2.03 Terms and Repayment. The Advances shall bear interest and be repaid in accordance with the terms and conditions set forth in the Basic Terms.

Section 2.04 Taxes. The Borrower shall pay any present or future stamp or documentary taxes or any other excise or property taxes, charges or similar levies that arise from any payment made hereunder or from the execution, delivery or registration of, performing under, or otherwise with respect to, this Agreement or any other Loan Document.

Section 2.05 Evidence of Debt. The Lender shall maintain in accordance with its usual practice an account or accounts evidencing the indebtedness of the Borrower to the Lender resulting from the Advances hereunder from time to time, including the amounts of principal and interest payable and paid to the Lender from time to time hereunder. Entries made in good faith by the Lender in such account or accounts shall be prima facie evidence of the amount of principal and interest due and payable or to become due and payable from the Borrower to the Lender under this Agreement, absent manifest error, provided, however, that the failure of the Lender to make an entry, or any finding that an entry is incorrect, in such account or accounts shall not limit or otherwise affect the obligations of the Borrower under the Note and this Agreement.

ARTICLE III

CONDITIONS TO EFFECTIVENESS AND LENDING

Section 3.01 Conditions Precedent to Effectiveness of this Agreement. This Agreement shall become effective on and as of, and the Lender shall be obligated to make the first of the Advances only on or after, the later of the date hereof or the first date on which all of the following conditions precedent have been satisfied (the "Effective Date"):

(a) The Borrower shall have identified the Designated Account and provided to the Lender all documentation reasonably required by the Lender to effect the ACH deposits and withdrawals hereunder, or in the alternative, the Borrower shall have provided the Lender with written wire instructions to effect a wire disbursement of deposits and withdrawals hereunder.

(b) The Borrower shall have established and/or funded, and pledged to the Lender, an account at Morgan Stanley Smith Barney in each case upon terms satisfactory to the Lender in its sole discretion**.**

(c) The Borrower shall have paid each of the required fees payable pursuant to the Basic Terms, if any, as well as any other expenses or other payment items set forth in Section 7.04(a) hereof or in any Closing Checklist that the Lender may have provided to the Borrower including, without limitation, any and all legal fees and disbursements of counsel to the Lender associated herewith.

(d) The Lender shall have received on or before the date of the first Advance to be made hereunder all of the documents listed on any Closing Checklist that the Lender may have provided to the Borrower, in addition to that which is set forth elsewhere in this Section 3.01, all in form and substance satisfactory to the Lender.

(e) The Lender shall have received such other approvals, opinions and documents as the Lender may reasonably request.

Upon satisfaction of such conditions, the Borrower hereby authorizes the Lender to insert, update or correct (a) any names, addresses and titles on behalf of the Borrower, the Lender or any other Loan Party in any Loan Document, (b) the date of each Loan Document, where required in such document, and (c) the effective interest rate and, as applicable, the repayment schedule in the Basic Terms hereof, whereupon the first Advance shall be made available to the Borrower in accordance with the terms and conditions hereof. At any time prior to the Effective Date, the Lender may, in its sole and absolute discretion, terminate any obligation it may have, if any, to execute and deliver this Agreement and make the Revolving Loan, whereupon any obligation of the Lender hereunder to make any Advance or in any other document executed in connection with any Advance shall terminate and be void and of no force and effect.

Section 3.02 Conditions Precedent to Each Advance under the Revolving Facility. The obligation of the Lender to make each Advance shall be subject to the satisfaction of the following conditions precedent before or concurrently with the making of such Advance:

(a) the following statements shall be true (and the acceptance by the Borrower of the proceeds of such Advance shall constitute a representation and warranty by the Borrower that on the date of any Advance such statements are true):

(i) the representations and warranties of the Borrower and each other Loan Party contained in Section 4.01 hereof and in each other Loan Document are correct on and as of the date of any Advance, before and after giving effect to such Advance and to the application of the proceeds therefrom, as though made on and as of such date, and

(ii) no event has occurred and is continuing, or would result from such Advance or from the application of the proceeds therefrom, that constitutes a Default; and

(b) the Lender shall have received such approvals, opinions and documents as the Lender may reasonably request.

ARTICLE IV

REPRESENTATIONS AND WARRANTIES

Section 4.01 Representations and Warranties of the Borrower. The Borrower represents and warrants to the Lender as follows:

(a) The Borrower: (i) is a corporation duly organized, validly existing and in good standing under the laws of the State, Commonwealth or other jurisdiction of its organization, (ii) is duly qualified and in good standing as a foreign business entity in each other jurisdiction in which it owns or leases property or in which the conduct of its business requires it to so qualify, and (iii) has all requisite power and authority (including, without limitation, all governmental licenses, agreements and other approvals) to own and lease and operate its properties and to carry on its business as now conducted and as proposed to be conducted. The Borrower's principal place of business is located in the State of California.

(b) The execution, delivery and performance by the Borrower of the Note, this Agreement and the other Loan Documents to which it is a party are within the Borrower's powers, have been duly authorized, by all necessary action, and (i) do not contravene the Borrower's charter or bylaws, operating agreement or partnership agreement, as the case may be, (ii) do not contravene any law or any contractual restriction binding on or affecting the Borrower, (iii) will not result in the breach of, or constitute a default or require any payment to be made under, any loan agreement, credit agreement, indenture, mortgage, deed of trust, bond, note, lease or other instrument or agreement binding on or otherwise affecting the Borrower or any of its properties, or (iv) except for the Liens created under the Loan Documents, will not result in or require the creation or imposition of any Lien upon or with respect to any of the properties of the Borrower.

(c) No authorization or approval or other action by, and no notice to or filing with, any governmental authority or regulatory body or any other third party is required for (i) the due execution, delivery and performance by the Borrower of the Loan Documents to which it is a party, or (ii) the granting by the Borrower of the Liens granted by it created pursuant to the Collateral Documents.

(d) The Note, this Agreement and the other Loan Documents to which the Borrower is a party have been duly executed and delivered by the Borrower, and are the legal, valid and binding obligations of the Borrower enforceable against the Borrower in accordance with their respective terms.

(e) There is no pending or threatened action, unsatisfied judgment or other proceeding affecting the Borrower before any court, governmental agency or arbitrator that (i) could be reasonably likely to have a Material Adverse Effect, or (ii) purports to affect the legality, validity or enforceability of the Note, this Agreement or any other Loan Document to which the Borrower is a party, or the consummation of the transactions contemplated hereby or thereby.

(f) The Borrower is not engaged in the business of extending credit for the purpose of purchasing or carrying margin stock (as defined in Regulation U), and no proceeds of any Advance will be used (i) to purchase or carry any margin stock (as defined in Regulation U) or to extend credit to others for the purpose of purchasing or carrying any margin stock, (ii) to repay any loan that was used to purchase or carry any margin stock, or (iii) to repay a loan made by an Affiliate of the Lender.

(g) "Isis Pharmaceuticals, Inc." is the proper legal name of the Borrower, and the Borrower is a corporation; and as of the date hereof, it has only those Subsidiaries and Major Affiliates listed on Schedule 4.01(g) hereof.

(h) Schedule 4.01(h) hereof sets forth Borrower's stockholders who beneficially own greater than 5% of Borrower's voting stock as disclosed pursuant to the Securities Exchange Act of 1934, and the ownership interest in Borrower's Subsidiaries.

(i) Schedule 4.01(i) hereof sets forth all of the Liens existing as of the date hereof filed against the Borrower, as debtor, and no such Liens are "adverse claims," as such term is defined in Section 8-102(a) of the Code.

(j) The Borrower, each other Loan Party and/or Subsidiary of the Borrower or any other Loan Party (and to Borrower's knowledge, each Major Affiliate), in each case to the extent required, (i) are in full compliance with and have policies, procedures, and internal controls in place that are reasonably designed to comply with applicable anti-corruption and anti-money laundering laws, rules and regulations, including, without limitation, the applicable provisions of the USA Patriot Act 2001, 107 Public Law 56 (October 26, 2001) (the "Patriot Act"), (ii) have implemented a Customer Identification Program ("CIP") and perform CIP due diligence in accordance with the Patriot Act, (iii) have policies and procedures reasonably designed to comply with Sections 312 and 319 of the Patriot Act, including the identification of beneficial ownership where required under applicable law, and (iv) have policies and procedures in place reasonably designed to prohibit accounts for foreign shell banks in compliance with Sections 313 and 319 of the Patriot Act.

(k) Neither the Borrower, any other Loan Party, and/or Subsidiary of the Borrower or any Loan Party (and to Borrower's knowledge, no Major Affiliate), nor any Person who, to the Borrower's knowledge, has or will have an interest in the transaction contemplated by this Agreement or will participate, in any manner whatsoever, in receiving or utilizing the proceeds of any Advance, whether directly or indirectly, is or has been a Politically Exposed Person or an Immediate Family Member or Close Associate of a senior political figure.

(l) Neither the Borrower, any other Loan Party, and/or Subsidiary of the Borrower or any Loan Party (and to Borrower's knowledge, no Major Affiliate), nor any director, officer, or employee thereof, nor, to the Borrower's knowledge, any, agent or representative thereof, is a Person that, or is owned or controlled by a Person that, (i) is the subject of any sanctions administered or enforced by the U.S. Department of Treasury's Office of Foreign Assets Control, the United Nations Security Council, the European Union or Her Majesty's Treasury (collectively, "Economic Sanctions"), (ii) is located, organized or resident in a country or territory that would be impermissible under any Economic Sanctions (including, without limitation, the countries and territories of Burma/Myanmar, Cuba, Iran, North Korea, Sudan and Syria) or (iii) has taken any action in furtherance of an offer, payment, promise to pay, or authorization or approval of the payment or giving of money, property, gifts or anything else of value, directly or indirectly, to any Person while knowing that all or some portion of the money or value will be offered, given or promised to anyone to improperly influence official action, to obtain or retain business or otherwise to secure any improper advantage

(m) The financial statements of the Borrower as at the end of the most recently ended fiscal year of the Borrower containing a balance sheet of the Borrower and the related statements of income and cash flow of the Borrower for the fiscal year then ended, duly certified by an Authorized Person of the Borrower, copies of which have been furnished to the Lender, fairly present the financial condition of the Borrower as at such date and the results of the operations of the Borrower for the period ended on such date, all in accordance with GAAP. Since the end of the most recently ended fiscal year there has been no Material Adverse Change with respect to the Borrower.

(n) All tax returns required to be filed by the Borrower in any jurisdiction have been filed, and all taxes, assessments, fees and other governmental charges upon the Borrower, or upon any of its property, income or franchises, which are shown to be due and payable on such returns have been paid. The Borrower is not aware of any proposed additional tax assessment or tax to be assessed against or applicable to the Borrower.

(o) The Borrower is solvent, is able to pay its debts as they become due and now owns property having a value both at fair valuation and a present fair salable value greater than the amount required to pay such debts as they mature, and will not be rendered insolvent, or be left with insufficient capital, or be unable to pay its debts as they mature, by the execution, delivery and performance of this Agreement or any other Loan Document to which the Borrower is a party or by the transactions contemplated hereunder or thereunder.

(p) The Borrower is not in default on any obligation for borrowed money, any purchase money obligation or other material lease, commitment, contract, instrument or other obligation, except as disclosed to Lender in writing.

(q) There is no event which constitutes a Default.

ARTICLE V

COVENANTS OF THE BORROWER

Section 5.01 Affirmative Covenants. So long as any portion of the Revolving Loan shall remain unpaid or the Lender shall have any Commitment hereunder, the Borrower will:

(a) Compliance with Laws, Etc. Comply in all material respects, with all applicable laws, rules, regulations and orders, such compliance to include, without limitation, compliance with ERISA, Regulation X and any and all applicable securities laws.

(b) Payment of Taxes, Etc. Pay and discharge before the same shall become delinquent, (i) all taxes, assessments and governmental charges or levies imposed upon it or upon its property and (ii) all lawful claims that, if unpaid, might by law become a Lien upon the Borrower's property; provided, however, that unless required by one of the Collateral Documents the Borrower shall not be required to pay or discharge any such tax, assessment, charge or claim that is being contested in good faith and by proper proceedings and as to which appropriate reserves are being maintained in accordance with GAAP by the Borrower, unless and until any Lien resulting therefrom attaches to its property and becomes enforceable against its other creditors.

(c) Maintenance of Insurance. (i) Maintain insurance with responsible and reputable insurance companies or associations in such amounts and covering such risks as is usually carried by companies engaged in similar businesses and owning similar properties in the same general areas in which the Borrower operates, and (ii) maintain insurance coverage which complies with the workers' compensation and employers' liability laws of all states in which the Borrower shall be required to maintain such insurance.

(d) Preservation of Organizational Existence, Etc. Preserve and maintain its existence, rights (charter and statutory) and franchises; including, without limitation, its legal name and jurisdiction of organization.

(e) Visitation Rights. Permit at any reasonable time and from time to time, the Lender or any agents or representatives thereof, upon reasonable advance notice to the Borrower, to examine and make copies of and abstracts from the records and books of account of, and visit the properties of the Borrower and to discuss the affairs, finances and accounts of the Borrower with any of its officers or directors and with their independent certified public accountants and financial advisors once per every rolling twelve (12) month period; provided, however, that if an Event of Default has occurred and is continuing, such limitation shall not apply and the Lender shall be entitled to make as many such inspections as it deems appropriate in its sole discretion and shall not be required to provide the Borrower or any other Person with prior notice of any such inspections.

(f) Keeping of Books. Keep proper books of record and account, in which full and correct entries shall be made of all financial transactions and the assets and business of the Borrower in accordance with GAAP.

(g) Maintenance of Properties, Etc. Maintain and preserve all of its properties that are used or useful in the conduct of its business (i) as required under any of the Collateral Documents, where applicable, and (ii) otherwise in good working order and condition, ordinary wear and tear excepted.

(h) Transactions with Major Affiliates. Conduct all transactions otherwise permitted under the Loan Documents with any of its Major Affiliates on terms that are fair and reasonable and no less favorable to the Borrower than it would obtain in a comparable arm's-length transaction with a Person not a Major Affiliate.

(i) Reporting Requirements. Furnish to the Lender:

(A) to the extent not publicly available, as soon as available and in any event no later than April 30st of each year, and if requested by the lender, the Borrower shall provide a complete SEC Form 10-K (annual report) containing the balance sheet, income statement, cash flows, notes to consolidated financial statements and Management's Discussion and Analysis, dated within four months of each April 30 (for avoidance of doubt, the next report will be due on or before April 30, 2016 for the year ending December 31, 2015);

(B) to the extent not publicly available, as soon as available and in any event within the earlier of (i) fifteen (15) days after the filing thereof, and if requested the lender, the Borrower shall provide a complete SEC Form 10-Q (quarterly report) containing the balance sheet, income statement, cash flows, notes to consolidated financial statements and Management's Discussion and Analysis, dated within forty-five (45) days of each quarter-end (for avoidance of doubt, the next report will be due on or before August 15, 2015 for the period ending June 31, 2015);

(C) as soon as possible and in any event within five (5) days after the occurrence of each Default and Event of Default continuing on the date of such statement, a statement of an Authorized Person of the Borrower setting forth details of such Default and Event of Default and the action that the Borrower has taken and proposes to take with respect thereto; and

(D) such other information respecting the Borrower, any Guarantor and each Grantor as the Lender may from time to time reasonably request.

(j) Cooperation. Take any action reasonably requested by Lender to carry out the intent of this Agreement.

(k) Use of Proceeds. Use proceeds of the Advances only to provide for general working capital non-purpose uses, other than to buy or carry margin stock or other securities.

(l) Patriot Act; Economic Sanctions. The Borrower will immediately notify the Lender in the event the Borrower is made aware or receives any notice that any of the Borrower, any Guarantor, or any Subsidiary or Major Affiliate of any Loan Party (or any of such Person's beneficial owners, trustees, members, managers, partners or affiliates or participants), or any Person who, to the Borrower's knowledge, has or will have an interest in the transaction contemplated by this Agreement or will participate, in any manner whatsoever, in receiving or utilizing the proceeds of any Advance, whether directly or indirectly (i) is or has been a Politically Exposed Person or an Immediate Family Member or Close Associate of a senior political figure or (ii) becomes the subject of any Economic Sanctions or the target of any governmental or regulatory matter involving Economic Sanctions.

(m) Further Assurances. Promptly upon request by the Lender, do, execute, acknowledge, deliver, record, re-record, file, re-file, register and re-register any and all such further acts, deeds, conveyances, pledge agreements, mortgages, deeds of trust, trust deeds, assignments, financing statements and continuations thereof, termination statements, notices of assignment, transfers, certificates, assurances and other instruments as the Lender may reasonably require from time to time in order to (i) carry out more effectively the purposes of the Loan Documents, (ii) to the fullest extent permitted by applicable law, subject the Borrower's properties, assets, rights or interests to the Liens now or hereafter intended to be covered by any of the Collateral Documents, (iii) perfect and maintain the validity, effectiveness and priority of any of the Collateral Documents and any of the Liens intended to be created thereunder and (iv) assure, convey, grant, assign, transfer, preserve, protect and confirm more effectively unto the Lender the rights granted or now or hereafter intended to be granted to the Lender under any Loan Document or under any other instrument executed in connection with any Loan Document to which the Borrower is or is to be a party.

Section 5.02 Negative Covenants. So long as any portion of the Revolving Loan shall remain unpaid or the Lender shall have any Commitment hereunder, the Borrower will not:

(a) [Reserved].

(b) Mergers, Etc. Merge or consolidate with or into, or convey, transfer, lease or otherwise dispose of (whether in one transaction or in a series of transactions) all or substantially all of its assets (whether now owned or hereafter acquired) to, any Person that does not simultaneously become a Guarantor of the Borrower's obligations hereunder (an additional "Guarantor") pursuant to documentation satisfactory to the Lender.

(c) [Reserved].

(d) Change in Nature of Business, Management or Ownership. Make any material change (i) in the nature of its business to a business other than research, development or commercialization of therapeutics or diagnostics, (ii) in its fiscal year, or (iii) to the legal name of any Grantor.

(e) Sales, Etc., of Assets. Sell, lease, license, transfer or otherwise dispose of any assets, or grant any option or other right to purchase, lease or otherwise acquire any assets other than (i) in exchange for consideration not less than fair market value of such assets; (ii) sales or licenses of intellectual property in the ordinary course of business, and (iii) as otherwise permitted under any of the Collateral Documents. The foregoing exceptions are further subject to compliance with the applicable Collateral Documents.

(f) Anti-Corruption and Anti-Money Laundering Laws; Economic Sanctions. Not, directly or indirectly, use the proceeds of any Advance, or lend, contribute or otherwise make available such proceeds to any Subsidiary or Major Affiliate of the Borrower or any other Loan Party or other Person: (i) to fund or facilitate any activities that would violate applicable anti-corruption or anti-money laundering laws, rules or regulations, including, without limitation, the Patriot Act, (ii) to fund or facilitate any activities or business of, or with, any Person or any country or territory that, at the time of such funding or facilitation, is the subject of Economic Sanctions, or (ii) in any manner that will result in a violation of Economic Sanctions by any Person, including, without limitation, the Lender.

Section 5.03 Financial Covenants. So long as any portion of the Revolving Loan shall remain unpaid or the Lender shall have any Commitment hereunder, the Borrower shall:

(a) Maximum Balance Sheet Leverage. Not permit the ratio of Total Unsubordinated Liabilities to Tangible Net Worth to exceed 3.00 to 1.00 at any time, measured on a quarterly basis.

(b) Debt Coverage Ratio. Maintain, as of the end of each fiscal year, for the four (4) quarters then ended, a ratio of (a) EBITDA plus Unencumbered Liquid Assets minus any and all amount declared or paid as a dividend, purchase, redemption, retirement, defeasement or other acquisition for value of any of the Borrower's capital stock to (b) the sum of the current maturities of all Debt for borrowed money (including, without limitation, current obligations under capital leases) plus interest expense, of not less than 1.50 to 1.00.

(c) Unencumbered Liquid Assets. Maintain at all times in an account at Lender or its Affiliates a minimum of $20,000,000.00 of Unencumbered Liquid Assets.

ARTICLE VI

EVENTS OF DEFAULT

Section 6.01 Events of Default. If any of the following events ("Events of Default") shall occur and be continuing:

(a) The Borrower shall fail to pay any principal of or interest on the Revolving Loan when the same becomes due and payable; or the Borrower shall fail to make any other payment of fees or other amounts payable under this Agreement when the same becomes due and payable (including, without limitation, prepayments required as a result of any event described in the "Collateral Maintenance" section of the Basic Terms); or

(b) Any representation or warranty made by the Borrower or any other Loan Party herein or in any other Loan Document, or any representation or warranty made by the Borrower or any other Loan Party (or any of their respective trustees, officers, members, managers or partners, as applicable) in connection with this Agreement or any other Loan Document, shall prove to have been incorrect or misleading in any material respect when made or as of the date of any Advance or the conversion date of any LIBO Rate Loan or SWAP Rate Loan; or

(c) (i) The Borrower shall fail to perform or observe any term, covenant or agreement contained in Sections 5.01 (other than Section 5.01(i)), 5.02, 5.03 or 7.11, or (ii) the Borrower or any other Loan Party shall fail to perform or observe any other term, covenant or agreement contained in this Agreement or any other Loan Document (except as set forth below in clause (iii) hereof) on its part to be performed or observed if such failure described in this subsection (c)(ii) shall remain unremedied for any grace period specified therein or for ten (10) days if no grace period is so specified or, in the case of a default under Section 5.01(f) or (g) hereof, ten (10) days after the Borrower or any other Loan Party had or should have had knowledge of such default, or (iii) the Borrower shall fail to timely cure a Curable Shortfall or immediately cure a Default Shortfall as required under the "Collateral Maintenance" section under the Basic Terms; or

(d) The Borrower or any other Loan Party shall fail to pay any principal of or premium or interest on any Debt of the Borrower or such other Loan Party (as the case may be), (A) to the Lender or any Affiliate of the Lender (other than Debt hereunder), or (B) to any other Person in an aggregate amount (for all Loan Parties together) of greater than or equal to $25,000,000.00 (other than indebtedness for borrowed money secured only by the real property to which the indebtedness relates and which is nonrecourse to the Borrower or such Loan Party), whether such indebtedness now exists or shall hereafter be created, (x) resulting in such indebtedness becoming or being declared due and payable or (y) constituting a failure to pay the principal and interest of any such indebtedness when due and payable at its stated maturity or required purchase or, subject to clause (x) above, upon declaration or acceleration or otherwise, and such acceleration shall not have been rescinded or annulled, or such failure to pay cured, within sixty (60) days after written notice to the Borrower by the Lender; or

(e) The Borrower or any other Loan Party, if an individual, shall die or be declared legally incompetent or shall voluntarily dissolve, liquidate or terminate operations, or shall generally not pay its debts as such debts become due, or shall admit in writing its inability to pay its debts generally, or shall make a general assignment for the benefit of creditors; or any proceeding shall be instituted by or against the Borrower or any other Loan Party seeking to adjudicate it a bankrupt or insolvent, or seeking liquidation, winding up, reorganization, arrangement, adjustment, protection, relief, or composition of it or its debts under any law relating to bankruptcy, insolvency or reorganization or relief of debtors, or seeking the entry of an order for relief or the appointment of a receiver, trustee, custodian or other similar official for it or for any substantial part of its property and, in the case of any such proceeding instituted against it (but not instituted by it), either such proceeding shall remain undismissed or unstayed for a period of ten (10) days, or any of the actions sought in such proceeding (including, without limitation, the entry of an order for relief against, or the appointment of a receiver, trustee, custodian or other similar official for, it or for any substantial part of its property) shall occur; or the Borrower or any other Loan Party shall take any action to authorize any of the actions set forth above in this subsection (e); or

(f) Any final judgment or order for the payment of money in excess of $25,000,000.00 (excluding any amounts covered by insurance) in the aggregate is rendered against Borrower, which judgment is not discharged or stayed within 60 days after (i) the date on which the right to appeal thereof has expired if no such appeal has commenced, or (ii) the date on which all rights to appeal have been extinguished; or

(g) [Reserved]; or

(h) (A)(i) Any Lien granted pursuant to any Collateral Document shall for any reason at any time cease to be a valid and perfected first priority lien on and security interest in the Collateral purported to be covered thereby and within ten (10) days of written notice from Lender to Borrower, Borrower fails to take the actions within Borrower's powers that are necessary to restore such lien; or (ii) any of the Collateral Documents shall for whatever reason be terminated or cease to be in full force and effect and within ten (10) days of written notice from Lender to Borrower, Borrower fails to take the actions within Borrower's powers that are necessary to restore such Collateral Document or (B) any Loan Party shall take any action to discontinue or to assert the invalidity or unenforceability of any Collateral Document; or

(i) [Reserved]; or

(j) The Borrower, any Guarantor, any Major Affiliate or Subsidiary of any of the Loan Parties shall (i) become the subject of any Economic Sanctions, (ii) become named on any list of persons who are or may be engaged in or who have been or may have been engaged in possible criminal activity or other wrongdoing, including, without limitation, money laundering or corruption or (iii) be indicted, arraigned or custodially detained on charges involving money laundering or corruption or any predicate crime to money laundering or corruption;

then, and in any such event, to the extent permitted by applicable law, the Lender may, by notice to the Borrower, (i) declare its obligation to make Advances to be terminated, whereupon the same shall forthwith terminate, (ii) declare the Advances, all interest thereon and all other amounts payable under this Agreement to be forthwith due and payable, whereupon the Advances and all such interest and all such other amounts shall become and be forthwith due and payable, without presentment, demand, protest or further notice of any kind, all of which are hereby expressly waived by the Borrower, (iii) take action to liquidate all or any part of the Collateral according to the procedures set forth in the Collateral Documents, and (iv) take any or all other remedial action permitted by applicable law; provided, however, that notwithstanding the foregoing, upon the occurrence of any event described in subsection (e) of this Section 6.01, (A) the obligation of the Lender to make Advances shall automatically be terminated and (B) the Advances and all such interest and all such amounts shall automatically become and be due and payable, without presentment, demand, protest or any notice of any kind, all of which are hereby expressly waived by the Borrower.

ARTICLE VII

MISCELLANEOUS

Section 7.01 Amendments, Etc. No amendment or waiver of any provision of this Agreement nor consent to any departure by the Borrower therefrom, shall in any event be effective unless the same shall be in writing and signed by the party to be charged thereby, and then such waiver or consent shall be effective only in the specific instance and for the specific purpose for which given.

Section 7.02 Notices, Etc. All notices and other communications provided for hereunder shall be in writing (including facsimile communication and any other method of communication authorized by the Lender, including, without limitation, electronic mail with respect to routine day-to-day notices) and mailed, faxed, or otherwise sent or delivered in accordance with the Basic Terms.

Section 7.03 No Waiver; Remedies. No failure on the part of the Lender to exercise, and no delay in exercising, any right hereunder shall operate as a waiver thereof; nor shall any single or partial exercise of any such right preclude any other or further exercise thereof or the exercise of any other right. The remedies herein provided are cumulative and not exclusive of any remedies provided by law.

Section 7.04 Costs and Expenses; Indemnification.

(a) The Borrower agrees to pay on demand all reasonable fees, costs and expenses of the Lender in connection with the preparation, negotiation, execution, delivery, administration, modification or amendment of any commitment letter issued by the Lender, this Agreement, the Note, the Collateral Documents and the other Loan Documents, including, without limitation, search, filing and recording fees and taxes, the reasonable fees and expenses of counsel for the Lender with respect thereto and with respect to advising the Lender as to its rights and responsibilities under such documents. The Borrower further agrees to pay on demand all fees, costs and expenses of the Lender, if any (including, without limitation, reasonable counsel fees and expenses), in connection with the enforcement (whether through negotiations, legal proceedings or otherwise) of this Agreement, the Note, the Collateral Documents and the other Loan Documents, including, without limitation, reasonable fees and expenses of counsel for the Lender in connection with the enforcement of rights under this Agreement, the Note, the other Loan Documents and this Section 7.04(a). The Borrower hereby authorizes the Lender and its Affiliates at any time and from time to time, upon prior notice to the Borrower (unless a Default or an Event of Default shall have occurred and be continuing, in which case no such notice shall be required), and whether or not the Lender shall have made any demand or an Event of Default shall have occurred, to charge any account of the Borrower maintained by the Lender or any of its Affiliates against such fees, costs and expenses. The rights of the Lender and its Affiliates under this Section are in addition to other rights and remedies (including, without limitation, rights of setoff) that the Lender and its Affiliates may have.

(b) The Borrower agrees to indemnify and hold harmless the Lender and each of its Affiliates and officers, directors, employees, agents and advisors (each, an "Indemnified Party") from and against any and all claims brought by a Third Party that are asserted or awarded against any Indemnified Party (together with damages, losses, liabilities and expenses, including, without limitation, reasonable fees and expenses of counsel, associated with such claims), in each case arising out of or in connection with or by reason of (including, without limitation, in connection with any investigation, litigation or proceeding or preparation of a defense in connection therewith) this Agreement, any of the transactions contemplated herein or the actual or proposed use of the proceeds of the Advances except to the extent such claim, damage, loss, liability or expense is found in a final, non-appealable judgment by a court of competent jurisdiction to have resulted from such Indemnified Party's gross negligence or willful misconduct. Notwithstanding the foregoing, the Borrower's indemnification obligations hereunder shall not apply with respect to any claim, damage, loss, liability or expense that is the result of an action brought by the Borrower directly against any Indemnified Party. In the case of an investigation, litigation or other proceeding to which the indemnity in this Section 7.04(b) applies, such indemnity shall be effective whether or not any Indemnified Party is otherwise a party thereto and whether or not the transactions contemplated hereby are consummated. After receipt by the Lender of written notice of any claim or the commencement of any action or proceeding against an Indemnified Party, the Lender shall give the Borrower written notice of such claim or the commencement of such action or proceeding (collectively, "Actions"), including a copy of such claim, process and all legal pleadings related to any such Action. The Lender shall be entitled to control the defense of any and all Actions using counsel of its own choosing, in its sole and absolute discretion, but the Borrower may, at its own cost and expense, participate in all such Actions with reputable counsel reasonably acceptable to the Lender. The Borrower may, at its own cost and expense, upon reasonable request, assist the Lender with respect to the defense of any Action, with the Lender's consent, not to be unreasonably withheld or delayed. Notwithstanding the foregoing, Borrower will not be liable for or be required to provide indemnification hereunder for any claim settled or disposed of without Borrower's prior written consent, not to be unreasonably withheld, conditioned or delayed. Each party hereto also agrees not to assert any claim against any other party hereto, or any of their Affiliates, or any of their respective directors, officers, employees, attorneys and agents, on any theory of liability, for special, indirect, consequential or punitive damages arising out of or otherwise relating to this Agreement, any of the transactions contemplated herein or the actual or proposed use of the proceeds of the Advances.

(c) Without prejudice to the survival of any other agreement of the Borrower hereunder, the agreements and obligations of the Borrower contained in this Section 7.04 shall survive the payment in full of principal, interest and all other amounts payable hereunder.

Section 7.05 Right of Setoff. Upon the occurrence and during the continuance of any Event of Default, the Lender and its Affiliates are hereby authorized at any time and from time to time, to the fullest extent permitted by law, to sell, liquidate, transfer or otherwise apply, or to cause to sell, liquidate, transfer or otherwise apply, any assets or securities of the Borrower held by Morgan Stanley Smith Barney, and set off and apply, or cause to set off and apply, any and all deposits (general or special, time or demand, provisional or final) at any time held and other indebtedness at any time owing by the Lender or any of its Affiliates to or for the credit or the account of the Borrower against any and all of the obligations of the Borrower now or hereafter existing under this Agreement or any other Loan Document, whether or not the Lender shall have made any demand under this Agreement or such other Loan Document. The rights of the Lender and its Affiliates under this Section are in addition to other rights and remedies (including, without limitation, other rights of setoff) that the Lender may have.

Section 7.06 Binding Effect; Successors and Assigns. This Agreement shall become effective on the Effective Date and thereafter shall be binding upon and inure to the benefit of the Borrower, the Lender and their respective successors and assigns.

Section 7.07 Governing Law. This Agreement shall be governed by, and construed in accordance with, the laws of the State of New York, without regard to conflicts of law principles of New York State law other than §5-1401 of the New York General Obligations Law.

Section 7.08 Execution in Counterparts. This Agreement may be executed in any number of counterparts and by different parties hereto in separate counterparts, each of which when so executed shall be deemed to be an original and all of which taken together shall constitute one and the same agreement. Delivery of an executed counterpart of a signature page to this Agreement by facsimile or other electronic means shall be effective as delivery of an original executed counterpart of this Agreement.

Section 7.09 Interest Rate Limitation. Anything herein to the contrary notwithstanding, if at any time the applicable interest rate, together with all fees and charges that are treated as interest under applicable law (collectively, the "Charges"), as provided for herein or in any other Loan Document, or otherwise contracted for, charged, received, taken or reserved by the Lender, shall exceed the maximum lawful rate (the "Maximum Rate") that may be contracted for, charged, taken, received or reserved by the Lender in accordance with applicable law, the rate of interest payable on the Advances, together with all Charges payable to the Lender, shall be limited to the Maximum Rate. Neither the Borrower nor any other Loan Party that is or will become liable for payment of the obligations of the Borrower under this Agreement shall be liable for unearned interest on the Advances or be required to pay interest thereon in excess of the maximum amount that may be lawfully charged under applicable law from time to time in effect, and the provisions of this Section 7.09 shall control over all other provisions of the Loan Documents that may be in conflict. If (a) the maturity of the obligations of the Borrower under this Agreement is accelerated for any reason, (b) any of such obligations are prepaid and as a result any amounts held to constitute interest are determined to be in excess of the legal maximum or (c) the Lender or any other holder of any or all of the obligations of the Borrower under this Agreement shall otherwise collect moneys that are determined to constitute interest that would otherwise increase the interest on any or all of such obligations to an amount in excess of that permitted to be charged by applicable law then in effect, then all such sums determined to constitute interest in excess of such legal limit shall, without penalty, be promptly applied to reduce the then outstanding principal of such obligations or, at the Lender's or such holder's option, be promptly returned to the Borrower or the other payor thereof upon such determination.

Section 7.10 Jurisdiction, Etc.

(a) Each of the parties hereto hereby irrevocably and unconditionally submits, for itself and its property, to the nonexclusive jurisdiction of any New York State court or federal court of the United States of America sitting in New York City, and any appellate court from any thereof, in any action or proceeding arising out of or relating to this Agreement or any other Loan Document, or for recognition or enforcement of any judgment, and each of the parties hereto hereby irrevocably and unconditionally agrees that all claims in respect of any such action or proceeding may be heard and determined in any such New York State court or, to the extent permitted by law, in such federal court. Each of the parties hereto consents to the service of copies of any and all process which may be served in any such action or proceeding by the mailing of copies of such process to such party at its address specified in the Basic Terms. Each of the parties hereto agrees that a final judgment in any such action or proceeding shall be conclusive and may be enforced in other jurisdictions by suit on the judgment or in any other manner provided by law. Nothing in this Agreement or any other Loan Document shall affect any right that any party may otherwise have to bring any action or proceeding relating to this Agreement or any other Loan Document in the courts of any other jurisdiction.

(b) Each of the parties hereto irrevocably and unconditionally waives, to the fullest extent it may legally and effectively do so, any objection that it may now or hereafter have to the laying of venue of any suit, action or proceeding arising out of or relating to this Agreement or any other Loan Document in any New York State or federal court. Each of the parties hereto hereby irrevocably waives, to the fullest extent permitted by law, the defense of an inconvenient forum to the maintenance of such action or proceeding in any such court.

Section 7.11 Assignments and Participations. The Borrower may not assign any of the Borrower's rights or obligations under this Agreement or any other Loan Document; provided, however, that:

(a) subject to Lender's prior written consent, not to be unreasonably withheld, conditioned or delayed, the Borrower may assign its rights or obligations under this Agreement or any other Loan Document in connection with a change of control so long as (i) the acquiring company shall have its senior unsecured debt rated by S&P and Moody's and such senior unsecured debt shall be rated at least BBB by S&P and at least Baa2 by Moody's and (ii) any successor entity agrees to be bound by the terms of this Agreement and each of the other Loan Documents; and

(b) the Borrower may also assign its rights or obligations under this Agreement or any other Loan Document in connection with a change of control with the Lender's consent, in its sole and absolute discretion, so long (x) as any successor entity agrees to be bound by the terms of this Agreement and each of the other Loan Documents and (y) the Borrower provides the Lender with written notice of such change of control, along with such information, that is sufficient, in the Lender's sole and absolute discretion, for the Lender to determine whether or not it would like to accept such assignee as a substitute Borrower hereunder, at least thirty (30) days prior to the consummation of such change of control. Notwithstanding anything in this subsection (b) to the contrary, if the Borrower provides the Lender with written notice of a change of control, along with the information required by clause (y) above less than thirty (30) days prior to the effectiveness of such change of control, the Lender shall have thirty (30) days to determine, in its sole and absolute discretion, whether or not to consent to the change of control or to require the Borrower to repay the principal amount of the Revolving Loan then outstanding, together with all fees, costs and expenses and accrued and unpaid interest thereon (a "Repayment Determination"). If the Lender delivers notice of a Repayment Determination to the Borrower, any purported assignment by the Borrower of its rights or obligations under this Agreement or any other Loan Document shall be ineffective, the Lender's obligation to make Advances shall immediately be terminated, and the Borrower shall repay the principal amount of the Revolving Loan then outstanding, together with all fees, costs and expenses and accrued and unpaid interest thereon as described in the prior sentence.

The Lender may assign to one or more Persons all or a portion of its rights and obligations under this Agreement (including, without limitation, all or a portion of its Commitment and the Advances owing to it), without notice to, or the consent of the Borrower or any other Loan Party; provided, however, that, other than assignments to (i) an Affiliate of the Lender, (ii) any entity or subdivision of the United States government and (iii) Federal Reserve Banks, which, for the avoidance of doubt shall not have a limit on the number of such assignments, the Lender shall not be permitted to assign such rights and obligations to more than three (3) Persons without the consent of the Borrower. The Lender may sell participations to one or more Persons (other than the Borrower or any other Loan Party or entity in which the Borrower has any direct or indirect equity interest, and not to exceed more than three (3) Persons without the Borrower's consent) in or to all or a portion of its rights and obligations under this Agreement (including, without limitation, all or a portion of its Commitment and the Advances owing to it). The Lender may, in connection with any assignment or participation or proposed assignment or participation pursuant to this Section 7.11, disclose to the assignee or participant or proposed assignee or participant, any information relating to the Borrower furnished to the Lender by or on behalf of the Borrower.

Section 7.12 WAIVER OF JURY TRIAL. EACH OF THE BORROWER AND THE LENDER HEREBY IRREVOCABLY WAIVES ALL RIGHT TO TRIAL BY JURY IN ANY ACTION, PROCEEDING OR COUNTERCLAIM (WHETHER BASED ON CONTRACT, TORT OR OTHERWISE) ARISING OUT OF OR RELATING TO THIS AGREEMENT OR ANY OTHER LOAN DOCUMENT, THE ADVANCES OR THE ACTIONS OF THE LENDER OR ANY OF ITS AFFILIATES IN THE NEGOTIATION, ADMINISTRATION, PERFORMANCE OR ENFORCEMENT HEREOF OR THEREOF.

Section 7.13 Severability of Provisions. Any provision of this Agreement which is prohibited or unenforceable in any jurisdiction shall, as to such jurisdiction, be ineffective to the extent of such prohibition or unenforceability without invalidating the remaining provisions of this Agreement or affecting the validity or enforceability of such provision in any other jurisdiction.

Section 7.14 Entire Agreement; Jointly Drafted. This Agreement, the other Loan Documents and all brokerage agreements to which the Borrower or any Major Affiliate of the Borrower is a party with Morgan Stanley Smith Barney constitute the entire agreement among the parties and supersede any prior written and verbal agreements among them with respect to the subject matter hereof and thereof. This Agreement shall be deemed to have been jointly drafted, and no provision of it shall be interpreted or construed for or against a party because such party purportedly prepared or requested such provision, any other provision, or this Agreement as a whole.

Section 7.15 Headings. Article, section and paragraph headings in this Agreement are included herein for convenience of reference only and shall not constitute a part hereof for any other purpose.

Section 7.16 Conflicts. Conflicts between this Agreement and any of the Collateral Documents shall be resolved in favor of the latter.

Section 7.17 Terms Generally. The definitions of terms herein shall apply equally to the singular and plural forms of the terms defined. Whenever the context may require, any pronoun shall include the corresponding masculine, feminine and neuter forms. The words "include," "includes" and "including" shall be deemed to be followed by the phrase "without limitation." The word "will" shall be construed to have the same meaning and effect as the word "shall." Unless the context requires otherwise (a) any definition of or reference to any agreement, instrument or other document herein shall be construed as referring to such agreement, instrument or other document as from time to time amended, supplemented or otherwise modified (subject to any restrictions on such amendments, supplements or modifications set forth herein), (b) any reference herein to any Person shall be construed to include such Person's successors and assigns, (c) the words "herein," "hereof" and "hereunder," and words of similar import, shall be construed to refer to this Agreement in its entirety and not to any particular provision hereof, (d) all references herein to Articles, Sections, Exhibits and Schedules shall be construed to refer to Articles and Sections of, and Exhibits and Schedules to, this Agreement, and (e) the words "asset" and "property" shall be construed to have the same meaning and effect and to refer to any and all tangible and intangible assets and properties, including cash, securities, accounts and contract rights.

Section 7.18 [Reserved].

Section 7.19 Tax Information. Notwithstanding anything herein to the contrary, the Borrower (and any employee, representative or other agent of the Borrower) may disclose to any and all Persons, without limitation of any kind, the U.S. federal income tax treatment and the U.S. federal income tax structure of the transactions contemplated hereby and all materials of any kind (including, without limitation, opinions or other tax analyses) that are provided to the Borrower (or any employee, representative or other agent of the Borrower) relating to such tax treatment and tax structure. However, no disclosure of any information relating to such tax treatment or tax structure may be made to the extent nondisclosure is reasonably necessary in order to comply with applicable securities laws.

Section 7.20 Other Events.

(a) In the event that any introduction of or change in applicable law, regulation, condition, directive or interpretation thereof (including, without limitation, any request, guideline or policy whether or not having the force of law and including, without limitation, Regulation D promulgated by the Board of Governors of the Federal Reserve System of the United States as now and from time to time hereafter in effect) by any authority charged with the administration or interpretation thereof:

(i) subjects the Lender to any tax with respect to any Advance (other than any tax on the overall net income of the Lender); or

(ii) changes the basis of taxation of payments to the Lender of principal of or interest on any Advance (other than any tax measured by or based upon the overall net income of the Lender); or

(iii) imposes, modifies or deems applicable any reserve or deposit requirements against any assets held by, deposits with or for the account of, or loans or commitments by, an office of the Lender in connection with the obligations of the Lender hereunder; or

(iv) imposes upon the Lender any other condition with respect to any amount paid or payable to or by the Lender pursuant to this Agreement;

and the result of any of the foregoing is to increase the cost to the Lender of maintaining the Commitment or to reduce the amount of any payment receivable by the Lender hereunder, or to require the Lender to make any payment on or calculated by reference to the gross amount of any sum received by it pursuant hereto, in each case by an amount which the Lender in its reasonable judgment deems material, then:

(A) the Lender shall promptly notify the Borrower in writing of the happening of such event;

(B) the Lender shall promptly deliver to the Borrower a certificate stating the change which has occurred or the reserve requirements or other conditions which have been imposed on the Lender or the request, direction or requirement with which it has complied, together with the date thereof, the amount of such increased cost, reduction or payment and the way in which such amount has been calculated; and

(C) the Borrower shall pay to the Lender, within thirty (30) days after delivery of the certificate referred to in clause (B) above, such an amount or amounts as will compensate the Lender for such additional cost, reduction or payment, only so long as the Lender is treating the Borrower with respect to such reimbursement request in a manner substantially similar to how it is treating its similarly situated borrowers under similar circumstances.

Without limitation of the foregoing, (i) if the Lender makes a demand for compensation pursuant to this paragraph (a), the Borrower may, notwithstanding anything in this Agreement to the contrary, upon notice to the Lender in accordance with Sections 2.03 and 7.02 not later than thirty (30) days following receipt of the certificate referred to in clause (B) above, repay in full the Advances together with accrued interest thereon to the date of prepayment (and, if Borrower timely makes such repayment in full, then no amount under clause (C) shall be owed); and (ii) notwithstanding anything in this Agreement to the contrary, (1) the Dodd Frank Wall Street Reform and Consumer Protection Act and all requests, rules, guidelines or directives thereunder or issued in connection therewith and (2) all requests, rules, guidelines or directives promulgated by the Bank for International Settlements, the Basel Committee on Banking Supervision (or any successor or similar authority) or the United States or foreign regulatory authorities, in each case pursuant to Basel III, shall in each case be deemed to be a "change in applicable law," regardless of the date enacted, adopted or issued.

(b) No failure on the part of the Lender to demand compensation under paragraph (a) above on any one occasion shall constitute a waiver of its right to demand such compensation on any other occasion, and no failure on the part of the Lender to deliver any certificate in a timely manner shall in any way reduce any obligation of the Borrower to the Lender under this Section. The protection of this Section shall be available to the Lender regardless of any possible contention of the invalidity or inapplicability of any law, regulation or other condition which shall give rise to any demand by the Lender for compensation hereunder.

Section 7.21 Capital Adequacy.

(a) If the Lender shall have determined that the applicability of any law, rule, regulation or guideline regarding capital adequacy, or any change in any of the foregoing or in the interpretation or administration of any of the foregoing by any governmental authority, central lender or comparable agency charged with the interpretation or administration thereof (and for purposes of this Agreement, (1) the Dodd-Frank Wall Street Reform and Consumer Protection Act and all regulations, guidelines and directions in connection therewith, and (2) all requests, rules, guidelines or directives promulgated by the Bank for International Settlements, the Basel Committee on Banking Supervision (or any successor or similar authority) or the United States or foreign regulatory authorities, in each case pursuant to Basel III, are, in each case, deemed to have been adopted and gone into effect after the date hereof), or compliance by the Lender (or any lending office of the Lender) or the Lender's holding company with any request or directive regarding capital adequacy (whether or not having the force of law) of any such authority, central lender or comparable agency, has or would have the effect of reducing the rate of return on the Lender's capital or on the capital of the Lender's holding company, if any, as a consequence of this Agreement or any Advance made by the Lender pursuant hereto to a level below that which the Lender or the Lender's holding company could have achieved but for such adoption, change or compliance (taking into consideration the Lender's policies and the policies of the Lender's holding company with respect to capital adequacy) by an amount deemed by the Lender to be material, then from time to time the Borrower shall pay to the Lender such additional amount or amounts as will compensate the Lender or the Lender's holding company for any such reduction suffered, only so long as the Lender is treating the Borrower with respect to such reimbursement request in a manner substantially similar to how it is treating its similarly situated borrowers under similar circumstances.

(b) A certificate of the Lender setting forth such amount or amounts as shall be necessary to compensate the Lender or its holding company as specified in paragraph (a) above shall be delivered to the Borrower and shall be deemed presumptively correct and binding on the Borrower absent manifest error. The Borrower shall pay the Lender the amount shown as due on any such certificate delivered by it within thirty (30) days after their receipt of the same. Without limitation of the foregoing, (i) if the Lender makes a demand for compensation pursuant to this clause (b), the Borrower may, notwithstanding anything in this Agreement to the contrary, upon notice to the Lender in accordance with Sections 2.03 and 7.02, not later than thirty (30) days following receipt of the certificate referred to in this clause (b), repay in full the Advances together with accrued interest thereon to the date of prepayment (and, if Borrower timely makes such repayment in full, then no amount under this clause (b) shall be owed).

(c) Failure on the part of the Lender to demand compensation for any reduction in return on capital with respect to any period shall not constitute a waiver of the Lender's right to demand such compensation with respect to such period or any other period. The protection of this Section shall be available to the Lender regardless of any possible contention of the invalidity or inapplicability of the law, rule, regulation, guideline or other change or condition which shall have occurred or been imposed.

Section 7.22 Survival. All covenants, agreements, representations and warranties made by the Borrower herein and in the certificates or other instruments delivered in connection with or pursuant to this Agreement shall be considered to have been relied upon by the Lender and shall survive the execution and delivery of the Note, this Agreement and the making of any Advance, regardless of any investigation made by the Lender or on its behalf and notwithstanding that the Lender may have had notice or knowledge of any Default, Event of Default or incorrect representation or warranty at the time any credit is extended hereunder, and shall continue in full force and effect as long as the principal of or any accrued interest on any Advance or any fee or any other amount payable under this Agreement is outstanding and so long as the Commitment has not expired or terminated. The provisions of Sections 7.04, 7.05, 7.10, 7.12, 7.19, 7.20, and 7.21 shall survive and remain in full force and effect regardless of payment in full of all Advances, the termination of the Commitment and the termination of this Agreement or any provision hereof.

Section 7.23 Credit Reports. For the avoidance of doubt and without in any way limiting any of the Lender's rights under any other Loan Document, including, without limitation, any financial statement and/or application delivered by or on behalf of any Loan Party with respect to the Revolving Facility, the Borrower authorizes the Lender to obtain credit reports on the Borrower from time to time until the Revolving Loans are paid in full and the Commitment has terminated, but not more often than annually except in connection with other extensions or proposed extensions of credit to the Borrower by the Lender or any of its Affiliates.

Section 7.24 Financial Advisor Disclaimer. The Borrower acknowledges and agrees that notwithstanding any advisory relationship that the Borrower may have with Morgan Stanley Smith Barney with respect to the Securities Account, no advisory relationship with Morgan Stanley Smith Barney exists with respect to the Revolving Facility and the Revolving Loan or in connection with the Borrower's decision to enter into this Agreement and the other Loan Documents, or the Borrower's decision to use the Securities Account as collateral for the Revolving Loan. The Borrower further acknowledges and agrees that neither Morgan Stanley Smith Barney, nor any financial advisor(s) to the Borrower employed by or working as an agent of Morgan Stanley Smith Barney, has acted or is acting as an investment advisor in connection with the Borrower's decision to enter into this Agreement and the other Loan Documents or the Borrower's decision to obtain the Revolving Loan and the Borrower is solely responsible for his, her or its decision to enter into this Agreement and to pledge assets in the Securities Account under the Security Agreement and the other Collateral Documents.

Section 7.25 Lender Affiliates. The Borrower acknowledges and agrees that it may not use proceeds of Advances to purchase any securities (a) issued by an affiliate (as defined under Regulation W) of the Lender (a "Regulation W Affiliate"), (b) in respect of which, and during any period that, any Regulation W Affiliate has acted as an underwriter, (c) sold by any Regulation W Affiliate acting as a principal, or (d) that would otherwise result in the Lender having to incur a capital charge under Regulation W or being in violation of Regulation W. If the Borrower makes a purchase in violation of the preceding sentence, Morgan Stanley Smith Barney may cancel or rescind such purchase at the sole cost of the Borrower, without any prior notice to the Borrower.

Section 7.26 Other Matters. The Borrower agrees not to use the Lender's or any of the Lender's Affiliates' name, logo, trademark or trade name in any marketing document or any communication with the public, including, without any limitation, a press release or tombstone, except as required by applicable law.

[Remainder of page intentionally left blank.]

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

ISIS PHARMACEUTICALS, INC.

By: */s/ Elizabeth L. Hougen*
Name: Elizabeth L. Hougen
Title: SVP Finance and CFO

MORGAN STANLEY PRIVATE BANK, NATIONAL ASSOCIATION

By: */s/ Jared Livingston*
Name: Jared Livingston
Title: Authorized Signatory

STATE OF _____

COUNTY OF _____

On this ___ day of _____, 2015, before me, the undersigned, personally appeared _____, personally known to me or proved to me on the basis of satisfactory evidence to be the individual whose name is subscribed to the within instrument, and acknowledged to me that **[he][she]** executed the same in **[his][her]** capacity as indicated therein.

_____
Notary Public

SCHEDULE I
TO LINE OF CREDIT AGREEMENT WITH
ISIS PHARMACEUTICALS, INC.

CERTAIN DEFINED TERMS

As used in this Agreement, the following terms shall have the following meanings:

"Advance" means an advance made pursuant to the Revolving Facility by the Lender to the Borrower under Article II.

"Affiliate" means, as to any Person, any other Person that, directly or indirectly, controls, is controlled by or is under common control with such Person or is a director or officer of such Person. For purposes of this definition, the term "control" (including the terms "controlling," "controlled by" and "under common control with") of a Person means the possession, direct or indirect, of the power to vote five percent (5%) or more of the voting stock (or equivalent) of such Person or to direct or cause the direction of the management and policies of such Person, whether through the ownership of voting stock (or the equivalent thereof), by contract or otherwise.

"Annex" has the meaning specified in Section 4.01(j).

"Authorized Person" means (a) with respect to any entity which is a limited liability company, a manager or authorized member thereof, (b) with respect to any entity which is a corporation, the chief financial officer thereof and, (c) with respect to any entity which is a partnership, the general partner thereof.

"Automatic ACH Payment" has the meaning specified in the Basic Terms.

"Basic Terms" has the meaning set forth in Section 1.02.

"Business Day" means a day of the year on which banks are not required or authorized by law to close in New York City.

"Charges" has the meaning specified in Section 7.09.

"CIP" has the meaning specified Section 4.01(j).

"Close Associate" means a Person who is widely and publicly known to maintain an unusually close relationship with a senior political figure, including a Person in a position to conduct substantial domestic and international financial transactions on behalf of such figure.

"Closing Checklist" means the Closing Checklist dated the date hereof prepared by the Lender and delivered to the Borrower setting forth the documents to be executed and/or delivered by the Loan Parties in connection with this Agreement.

"Code" means the Uniform Commercial Code as enacted in the State of New York, as amended from time to time.

"Collateral" means all "Collateral" referred to in the Collateral Documents and all other property that is or is intended to be subject to any Lien in favor of the Lender.

"Collateral Documents" means, collectively, the Security Agreement, all financing statements with respect to the Collateral and any other Loan Document pursuant to which any Collateral is granted to the Lender by any Loan Party.

"Commitment" means the obligation of the Lender to make Advances to the Borrower in an amount up to the lesser of (i) $20,000,000.00 or (ii) an amount equal to the sum of the amounts obtained by multiplying the aggregate Market Value of each type of Collateral in the Securities Account set forth in Column A of Exhibit A hereto times the corresponding percentage specified in Column B of Exhibit A hereto with respect to each such type of Collateral in the Securities Account, all on the terms and conditions set forth in this Agreement.

"Curable Shortfall" has the meaning specified in the Basic Terms.

"Debt" of any Person means, without duplication, (a) all indebtedness of such Person for borrowed money or for the deferred purchase price of property or services (other than current trade payables incurred in the ordinary course of business), (b) all obligations of such Person evidenced by notes, bonds, debentures or other similar instruments, (c) all capital lease obligations of such Person, (d) all obligations of such Person, contingent or otherwise, in respect of acceptances, letters of credits or similar extensions of credit, (e) all liabilities secured by any Lien on any property owned by such Person, even though such Person has not assumed or otherwise become liable for the payment thereof, (f) all obligations of such Person in respect of interest rate or currency protection agreements, (g) all Debt of one or more others guaranteed directly or indirectly in any manner by such Person, and (h) trade debt which is more than ninety (90) days past due.

"Default" means any Event of Default or any event that would constitute an Event of Default but for the requirement that notice be given or time elapse or both.

"Default Rate" has the meaning specified in the Basic Terms.

"Default Shortfall" has the meaning specified in the Basic Terms.

"Default Shortfall Cure Amount" has the meaning specified in the Basic Terms.

"Designated Account" means, in respect of the Borrower, that certain deposit account which may be established and maintained by the Borrower at a financial institution, the account number and location of which shall be provided to the Lender pursuant to the Basic Terms set forth herein.

"EBITDA" means net income (net loss) exclusive of extraordinary gains, if any, plus (a) interest expense, (b) income tax expense, (c) depreciation expense and (d) amortization expense.

"Economic Sanctions" has the meaning specified in Section 4.01(l).

"Effective Date" has the meaning specified in Section 3.01.

"Events of Default" has the meaning specified in Section 6.01.

"Fixed LIBO Rate" has the meaning specified in the Basic Terms.

"Fixed SWAP Rate" has the meaning specified in the Basic Terms.

"GAAP" means the generally accepted accounting principles in the United States, consistently applied, or any successor principles.

"Grantor(s)" means the Borrower and any other Person pledging collateral to secure the obligations of the Borrower under this Agreement.

"Guarantor(s)" means any Person providing a guaranty in favor of the Lender with respect to the Borrower's obligations under this Agreement.

"Guaranty" means any guaranty agreement in favor of the Lender in connection with this Agreement.

"Immediate Family Member" means, but is not limited to, a Person's parents, siblings, children and in-laws.

"Indemnified Party" has the meaning specified in Section 7.04(b).

"Intangible Assets" means goodwill, intellectual property (licenses, patents, trademarks, trade names, copyrights, service marks and brand names), experimental expenses, organization expense and any other assets that are properly classified as intangible assets in accordance with GAAP.

"Interest Period" means, (i) in respect of each LIBO Rate Loan, the period commencing on the date such LIBO Rate Loan is advanced, converted to or continued as a LIBO Rate Loan and ending on such date that is either one (1), two (2), three (3), four (4), six (6), or twelve (12) months thereafter and (ii) in respect of each SWAP Rate Loan, the period commencing on the date such SWAP Rate Loan is advanced, converted to or continued as a SWAP Rate Loan and ending on the date that is three (3) or five (5) years thereafter, but in no event later than the Termination Date; provided that, (a) any Interest Period that would otherwise end on a day that is not a Business Day shall be extended to the next succeeding Business Day unless such Business Day falls in another calendar month, in which case such Interest Period shall end on the next preceding Business Day; (b) any Interest Period that begins on the last Business Day of a calendar month (or on a day for which there is no numerically corresponding day in the calendar month at the end of such Interest Period) shall end on the last Business Day of the calendar month at the end of such Interest Period; and (c) no Interest Period shall extend beyond the Termination Date.

"Internal Revenue Code" means the Internal Revenue Code of 1986, as amended from time to time, and the regulations promulgated and rulings issued thereunder.

"Letter of Interest" means that certain Letter of Interest dated July 14, 2014 by and between the Lender and the Borrower.

"LIBO Rate" means, for any day, an interest rate per annum equal to the interest rate set forth on the key rates page of www.bloomberg.com as the ICE Benchmark Administration's (or its successor's) London Interbank Offered Rate (LIBOR) (or an equivalent rate) for the applicable interest period for such day, or, if such interest rate shall not be so set forth for such day, for the then most recent day for which such interest rate is so set forth.

"LIBO Rate Loan" means those Advances bearing a fixed interest rate for a specific Interest Period based on the LIBO Rate for that Interest Period.

"Lien" means any lien, security interest, adverse claim or other charge or encumbrance of any kind, or any other type of preferential arrangement having the effect of a lien or security interest, including, without limitation, the lien or retained security title of a conditional vendor and any easement, right of way or other encumbrance on title to real property.

"Loan Documents" means this Agreement, the Note, the Collateral Documents, the Guaranty, and any other document entered into in connection herewith other than any commitment letter entered into with respect to the financing governed by this Agreement, in each case as amended, supplemented or otherwise modified from time to time.

"Loan Party" means any of the Borrower, any Guarantor, any Grantor and any other Person required to become a Guarantor of the Advances pursuant to the terms of this Agreement and/or any Guaranty.

"Major Affiliate" means, as to any Person, any other Person that is a director or officer of such Person, or is an "insider" of such Person for purposes of the Securities Exchange Act of 1934.

"Margin" has the meaning specified in the Basic Terms.

"Market Value" means the value of the Collateral held in the Securities Account as determined by the following standards: (a) marketable securities shall be determined by reference to the most recent closing bid price reported by the applicable securities exchange or quoted by the National Association of Securities Dealers Automated Quotation System or such other basis as the Lender may determine and (b) cash equivalents on any day shall be determined by reference to the most recent closing bid price reported by the applicable exchange or on such other basis as the Lender may determine.

"Material Adverse Change" means any material adverse change in (a) the business, condition (financial or otherwise), operations, performance, properties or prospects of any Loan Party or (b) the value of the Collateral.

"Material Adverse Effect" means a material adverse effect on (a) the business, condition (financial or otherwise), operations, performance, properties or prospects of any Loan Party, (b) the rights or remedies of the Lender under this Agreement or the other Loan Documents, (c) the ability of any Loan Party to perform any of its obligations under any Loan Document to which it is a party or (d) the value of the Collateral.

"Maximum Rate" has the meaning specified in Section 7.09.

"Monthly LIBO Rate" means, for any day, the one-month LIBO Rate.

"Moody's" means Moody's Investors Service, Inc.

"Morgan Stanley Smith Barney" means Morgan Stanley Smith Barney LLC, a Delaware limited liability company, any of its Affiliates (including, without limitation, the Lender) or any successor thereof.

"Note" has the meaning specified in Section 2.01.

"Patriot Act" has the meaning specified in Section 4.01(j).

"Person" means an individual, partnership, corporation (including a business trust), joint stock company, trust, unincorporated association, joint venture, limited liability company or other entity, or a government or any political subdivision or agency thereof.

"Politically Exposed Person" means a senior official in the executive, legislative, administrative, military or judicial branch of a government (whether elected or not) or a major political party, a senior executive of a government-owned corporation or a corporation, business or other entity formed by, or for the benefit of, such a figure.

"Prepayment Premium" shall mean, for any prepayment of any LIBO Rate Loan or SWAP Rate Loan, a premium (as liquidated damages and not as a penalty) equal to the greater of (i) $500.00 and (ii) the amount necessary, in the Lender's sole and absolute discretion, to compensate the Lender for any losses, costs or expenses that the Lender may incur as a result of such prepayment including, without limitation, any loss (including loss of anticipated profit), cost or expense incurred by reason of the liquidation or redeployment of deposits or other funds acquired by the Lender to fund and/or hedge such Loan.

"Prime Rate" means, for any day, an interest rate per annum equal to the interest rate set forth on the key rates page of www.bloomberg.com as the Prime Rate (or an equivalent rate) for such day, or, if such interest rate shall not be so set forth for such day, for the then most recent day for which such interest rate is so set forth.

"Regulation U" means Regulation U promulgated by the Board of Governors of the Federal Reserve System of the United States, as now and from time to time hereafter in effect.

"Regulation W" means Regulation W promulgated by the Board of Governors of the Federal Reserve System of the United States, as now and from time to time hereafter in effect.

"Regulation W Affiliate" has the meaning specified in Section 7.25.

"Regulation X" means Regulation X promulgated by the Board of Governors of the Federal Reserve System of the United States, as now and from time to time hereafter in effect.

"Revolving Facility" means the line of credit facility extended by the Lender to the Borrower hereunder.

"Revolving Loan" means the outstanding principal amount of all Advances.

"S&P" means, Standard & Poor's Ratings Services, a division of the McGraw Hill Companies, Inc.

"Securities Account" means the account maintained by the Borrower with Morgan Stanley Smith Barney bearing Account No. 109-051983, together with any successor account(s), including, without limitation, any other such account(s) maintained by a Grantor held by Morgan Stanley Smith Barney that is/are custodied and carried on the books of Morgan Stanley Smith Barney that replace(s) or is/are established to supplement the aforesaid numbered account.

"Security Agreement" means the Financial Assets Security Agreement, dated as of the date hereof, made by the Borrower in favor of the Lender.

"Shortfall" has the meaning specified in the Basic Terms.

"Shortfall Cure Amount" has the meaning specified in the Basic Terms.

"Subordinated Debt" means Debt subordinated to the Borrower's obligations to the Lender pursuant to a subordination agreement in form and substance satisfactory to the Lender.

"Subsidiary" of any Person means any corporation, partnership, joint venture, limited liability company, trust or estate of which (or in which) more than fifty percent (50%) of (a) the issued and outstanding voting stock of such corporation, (b) the interest in the capital or profits of such limited liability company, partnership or joint venture or (c) the beneficial interest in such trust or estate is at the time directly or indirectly owned or controlled by such Person, by such Person and one or more of its other Subsidiaries or by one or more of such Person's other Subsidiaries.

"SWAP Rate" means, for any day, an interest rate per annum equal to the interest rate shown on the Bloomberg service "USSW" screen as the LIBOR swap rate (or an equivalent rate) on such day for the selected interest period or, if such interest rate shall not be so set forth for such day, for the then most recent day for which such interest rate is so set forth.

"SWAP Rate Loan" means those Advances bearing a fixed interest rate for a specific Interest Period based on the SWAP Rate for that Interest Period.

"Tangible Net Worth" means Total Tangible Assets minus Total Liabilities.

"Termination Date" means the earlier of (a) May ___, 2020 and (b) the date of termination in whole of the Commitment pursuant to Section 6.01 or 7.11.

"Total Liabilities" means all liabilities, including (i) capitalized leases, (ii) Subordinated Debt, and (iii) all reserves for deferred taxes and other deferred sums appearing on the liabilities side of the balance sheet of a Person.

"Total Tangible Assets" means all assets excluding the aggregate amount of Intangible Assets.

"Total Unsubordinated Liabilities" means Total Liabilities minus Subordinated Debt.

"Unencumbered Liquid Assets" means unrestricted cash and unrestricted marketable securities acceptable to the Lender in its sole discretion (excluding any cash or marketable securities credited to or held in an Individual Retirement Account or other similar retirement investment account), which can be converted to cash within five (5) Business Days, in either case without the consent of any Person and on which there is no Lien, which may be tested by the Lender in its sole discretion.

"United States Dollars" means lawful money of the United States of America.

SCHEDULE 4.01(g)

TO LINE OF CREDIT AGREEMENT WITH
ISIS PHARMACEUTICALS, INC.

SUBSIDIARIES/MAJOR AFFILIATES

Subsidiaries (all Wholly-Owned by Isis)

Isis USA Limited, a United Kingdom Limited Private Company

PerIsis I Development Corporation, a Delaware Corporation

Symphony GenIsis, Inc., a Delaware Corporation

Akcea Therapeutics, Inc., a Delaware Corporation

Major Affiliates

Spencer R. Berthelsen

Breaux B. Castleman

Stanley T. Crooke

Joseph Klein, III

Joseph Loscalzo

Frederick T. Muto(1)

B. Lynne Parshall

Joseph H. Wender

C. Frank Bennett

Sarah Boyce

Richard S. Geary

Elizabeth L. Hougen

Brett P. Monia

Patrick R. O'Neil

FMR LLC

SCHEDULE 4.01(h)

TO LINE OF CREDIT AGREEMENT WITH
ISIS PHARMACEUTICALS, INC.

OWNERSHIP

Owner	**Entity**	**Percentage**
FMR LLC	Isis Pharmaceuticals, Inc.	15.0%(1)
BlackRock, Inc.	Isis Pharmaceuticals, Inc.	8.0%(1)
ClearBridge Investments, LLC	Isis Pharmaceuticals, Inc.	7.6%(1)
The Vanguard Group	Isis Pharmaceuticals, Inc.	6.1%(1)
BB Biotech AG	Isis Pharmaceuticals, Inc.	5.0%(1)
Isis Pharmaceuticals, Inc.	Isis USA Limited	100%
Isis Pharmaceuticals, Inc.	PerIsis I Development Corporation	100%
Isis Pharmaceuticals, Inc.	Symphony GenIsis, Inc.	100%
Isis Pharmaceuticals, Inc.	Akcea Therapeutics, Inc.	100%

(1) Based on most recent filings with the SEC

SCHEDULE 4.01(i)

TO LINE OF CREDIT AGREEMENT WITH
ISIS PHARMACEUTICALS, INC.

EXISTING LIENS

Isis has existing Liens related to equipment leases or financing pursuant to which Isis has granted a security interest in the applicable equipment (and related software/consumables), but not a security interest in any Collateral under this Agreement, each as further described in the UCC-1 reports Isis has provided Lender by separate cover. The secured parties under such Liens are:

- Beckman Coulter Inc.
- General Electric Capital Corporation
- Fleet Capital Corporation
- Cisco Systems Capital Corporation
- RBS Asset Finance, Inc.
- Navitas Lease Corp.

EXHIBIT A

TO LINE OF CREDIT AGREEMENT WITH
ISIS PHARMACEUTICALS, INC.

SECURITIES ACCOUNT COLLATERAL MAINTENANCE GUIDELINES

Column A	**Column B**	**Column C**	**Column D**
Type of Pledged Collateral **(Note: Any security not specifically listed, and all securities issued by Morgan Stanley or its affiliates, shall be deemed ineligible.)**	**Loanable Value**	**Margin Call**	**Sell-Out**
(1) Cash, Cash Equivalents, Commercial Paper and Banker's Acceptances rated A1 / P1, Money Market Funds, and FDIC-insured, brokered CDs with maturities less than 5yrs	97%	98%	99%
(2) Government Obligations (Direct or Guaranteed), US Treasury Bills, Notes, Bonds and Strips, US Government Agencies (e.g FHLB, FFCB) and related MBS/CMO's, US Treasury Mutual Funds, and Pre-refunded Bonds collateralized by any of these securities (a) Tenor less than 5 years (b) Tenor 5-9 years (c) Tenor 10-19 years (d) Tenor 20+ years	 96% 94% 92% 90%	 96% 94% 93% 91%	 97% 95% 94% 92%
(3) All other US Government Agency Debt (e.g. FNMA, FHLMC): (a) Tenor less than 5 years (b) Tenor 5-9 years (c) Tenor 10-19 years (d) Tenor 20+ years	 96% 92% 88% 82%	 96% 93% 90% 85%	 97% 95% 92% 89%
(4) State and Municipal Obligations with no position > 15% of the current outstanding issuance** (a) rated* AAA through BBB- (b) rated* BB+ or BB	 84% 70%	 87% 73%	 89% 76%
(5) Non-Convertible Corp Bonds with a price ≥$40, a current outstanding issuance of at least $25 million, and no position >15% of the issue size (a) rated* AAA through AA- (b) rated* A+ through BBB- (c) rated* BB+ or BB	 89% 84% 70%	 92% 87% 73%	 94% 89% 76%
(6) Municipal Bond and Corporate Bond Mutual Funds trading >=$4/sha (open end after 30-days and closed end)	80%	83%	86%
(7) Convertible Corp Bonds with a price ≥$40, a current outstanding issuance of at least $25 million, and no position >15% of the issue size	72%	75%	78%

(8) Diversified Common, Preferred and Convertible Preferred Equities and Unit Investment Trusts trading on a National Securities Exchange as defined by the Securities Exchange Act of 1934:**			
(a) >= $10.00/sha	75%	78%	80%
(b) $9.00-$9.99/sha	60%	65%	70%
(c) $8.00-$8.99/sha	50%	60%	65%
(d) $7.00-$7.99/sha	50%	55%	60%
(e) $4.00-$6.99/sha	50%	53%	55%
(9) Diversified ADRs trading >= $10/sha on a National Securities Exchange as defined by the Securities Exchange Act of 1934:**	75%	78%	80%
(10) Balanced and Diversified Stock Mutual Funds (open end after 30-days and closed end) and Exchange Traded Funds. On-shore funds only.			
(a) >=$4/sha	80%	83%	86%
(b) $2.00-$3.99/sha	0%	70%	74%
(11) Specialized / Sector and International Mutual Funds and ETFs >=$4/sha. Includes High Yield, levered or inverse Mutual Funds and ETFs.	70%	73%	76%

* The lower of Moody's or S&P.
** Thereafter, no one issuer of equity securities covered by row 8 represents more than 25% of the long market value of the collateral.

Credit Risk Management reserves the right to decrease these percentages as warranted on a case by case basis.

EXHIBIT 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Isis Pharmaceuticals, Inc.;

2. Based on my knowledge, this quarterly report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this quarterly report;

3. Based on my knowledge, the condensed consolidated financial statements, and other financial information included in this quarterly report, fairly present in all material respects the financial condition, condensed consolidated results of operations and condensed consolidated cash flows of the registrant as of, and for, the periods presented in this quarterly report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: August 4, 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: August 4, 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 June 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: August 4, 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.