**UNITED STATES**
**SECURITIES AND EXCHANGE COMMISSION**
**Washington, DC 20549**

**Form 10-Q**

**(Mark One)**

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

**For the Quarterly Period Ended September 30, 2014**

**OR**

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

**For the transition period from to**

**Commission file number 0-19125**

**Isis Pharmaceuticals, Inc.**
(Exact name of Registrant as specified in its charter)

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

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

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

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

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

**Common Stock, $.001 Par Value**

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

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

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

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

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

The number of shares of voting common stock outstanding as of November 5, 2014 was 118,141,113.

**ISIS PHARMACEUTICALS, INC.**
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**TRADEMARKS**

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

**Regulus Therapeutics™ is a trademark of Regulus Therapeutics Inc.**

**KYNAMRO® is a registered trademark of Genzyme Corporation**

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

| | September 30, 2014 (Unaudited) | December 31, 2013 |
|---|---|---|
| **ASSETS** | | |
| Current assets: | | |
| Cash and cash equivalents | $ 73,220 | $ 159,973 |
| Short-term investments | 518,766 | 496,788 |
| Contracts receivable | 26,313 | 11,102 |
| Inventories | 7,085 | 8,033 |
| Investment in Regulus Therapeutics Inc. | 47,426 | 52,096 |
| Other current assets | 8,353 | 7,518 |
| Total current assets | 681,163 | 735,510 |
| Property, plant and equipment, net | 88,068 | 86,198 |
| Licenses, net | 3,160 | 4,572 |
| Patents, net | 16,879 | 15,517 |
| Deposits and other assets | 4,533 | 5,359 |
| Total assets | $ 793,803 | $ 847,156 |
| **LIABILITIES AND STOCKHOLDERS' EQUITY** | | |
| Current liabilities: | | |
| Accounts payable | $ 15,627 | $ 11,009 |
| Accrued compensation | 7,164 | 12,168 |
| Accrued liabilities | 29,140 | 22,092 |
| Current portion of long-term obligations | 3,667 | 4,408 |
| Current portion of deferred contract revenue | 51,727 | 48,135 |
| Total current liabilities | 107,325 | 97,812 |
| Long-term deferred contract revenue | 110,614 | 142,790 |
| 2¾ percent convertible senior notes | 155,437 | 150,334 |
| Long-term obligations, less current portion | 4,039 | 6,542 |
| Long-term financing liability for leased facility | 71,616 | 71,288 |
| Total liabilities | 449,031 | 468,766 |
| Stockholders' equity: | | |
| Common stock, $0.001 par value; 300,000,000 shares authorized, 117,990,371 and 116,471,371 shares issued and outstanding at September 30, 2014 and December 31, 2013, respectively | 118 | 116 |
| Additional paid-in capital | 1,365,407 | 1,324,804 |
| Accumulated other comprehensive income | 16,894 | 21,080 |
| Accumulated deficit | (1,037,647) | (967,610) |
| Total stockholders' equity | 344,772 | 378,390 |
| Total liabilities and stockholders' equity | $ 793,803 | $ 847,156 |

See accompanying notes.

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

| | Three Months Ended September 30, | | Nine Months Ended September 30, | |
|---|---|---|---|---|
| | **2014** | **2013** | **2014** | **2013** |
| Revenue: | | | | |
| Research and development revenue under collaborative agreements | $ 43,798 | $ 23,258 | $ 119,975 | $ 102,543 |
| Licensing and royalty revenue | 265 | 327 | 9,325 | 2,493 |
| Total revenue | 44,063 | 23,585 | 129,300 | 105,036 |
| Expenses: | | | | |
| Research, development and patent expenses | 61,086 | 45,660 | 173,798 | 126,603 |
| General and administrative | 4,470 | 3,430 | 13,313 | 10,241 |
| Total operating expenses | 65,556 | 49,090 | 187,111 | 136,844 |
| Loss from operations | (21,493) | (25,505) | (57,811) | (31,808) |
| Other income (expense): | | | | |
| Investment income | 675 | 434 | 2,003 | 1,400 |
| Interest expense | (4,998) | (4,867) | (14,902) | (14,470) |
| Gain on investments, net | 538 | 175 | 675 | 2,073 |
| Loss before income tax (expense) benefit | (25,278) | (29,763) | (70,035) | (42,805) |
| Income tax (expense) benefit | (1,398) | 5,193 | (2) | 6,437 |
| Net loss | $ (26,676) | $ (24,570) | $ (70,037) | $ (36,368) |
| Basic and diluted net loss per share | $ (0.23) | $ (0.21) | $ (0.60) | $ (0.33) |
| Shares used in computing basic and diluted net loss per share | 117,811 | 115,263 | 117,511 | 108,608 |

See accompanying notes.

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

| | Three Months Ended September 30, | | Nine Months Ended September 30, | |
|---|---|---|---|---|
| | 2014 | 2013 | 2014 | 2013 |
| Net loss | $ (26,676) | $ (24,570) | $ (70,037) | $ (36,368) |
| Unrealized (losses) gains on securities, net of tax | (6,994) | 2,207 | (3,189) | 17,876 |
| Reclassification adjustment for realized gains included in net loss | (831) | (172) | (997) | (1,335) |
| Comprehensive loss | $ (34,501) | $ (22,535) | $ (74,223) | $ (19,827) |

See accompanying notes.

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

| | Nine Months Ended September 30, | |
|---|---|---|
| | **2014** | **2013** |
| **Operating activities:** | | |
| Net loss | $ (70,037) | $ (36,368) |
| Adjustments to reconcile net loss to net cash (used in) provided by operating activities: | | |
| Depreciation | 4,791 | 4,995 |
| Amortization of patents | 841 | 891 |
| Amortization of licenses | 1,412 | 1,531 |
| Amortization of premium on investments, net | 5,649 | 3,742 |
| Amortization of debt issuance costs | 412 | 308 |
| Amortization of 23¤4 percent convertible senior notes discount | 5,103 | 4,715 |
| Amortization of long-term financing liability for leased facility | 4,962 | 4,919 |
| Stock-based compensation expense | 22,894 | 8,318 |
| Gain on investments, net | (675) | (2,073) |
| Non-cash losses related to patents, licensing and property, plant and equipment | 753 | 429 |
| Changes in operating assets and liabilities: | | |
| Contracts receivable | (15,211) | (12,123) |
| Inventories | 948 | (1,264) |
| Other current and long-term assets | (1,239) | (1,535) |
| Accounts payable | 1,414 | (2,293) |
| Accrued compensation | (5,004) | (1,225) |
| Deferred rent | 126 | 173 |
| Accrued liabilities | 7,046 | 443 |
| Deferred contract revenue | (28,584) | 104,402 |
| Net cash (used in) provided by operating activities | (64,399) | 77,985 |
| | | |
| **Investing activities:** | | |
| Purchases of short-term investments | (250,580) | (303,862) |
| Proceeds from the sale of short-term investments | 222,896 | 135,130 |
| Purchases of property, plant and equipment | (3,969) | (1,113) |
| Acquisition of licenses and other assets, net | (2,443) | (2,721) |
| Proceeds from the sale of strategic investments | 2,036 | 2,110 |
| Net cash used in investing activities | (32,060) | (170,456) |
| | | |
| **Financing activities:** | | |
| Proceeds from equity awards | 17,709 | 56,898 |
| Net proceeds from public common stock offering | - | 173,292 |
| Proceeds from equipment financing arrangement | - | 2,513 |
| Principal payments on debt and capital lease obligations | (8,003) | (8,306) |
| Net cash provided by financing activities | 9,706 | 224,397 |
| | | |
| Net (decrease) increase in cash and cash equivalents | (86,753) | 131,926 |
| Cash and cash equivalents at beginning of period | 159,973 | 124,482 |
| Cash and cash equivalents at end of period | $ 73,220 | $ 256,408 |
| | | |
| **Supplemental disclosures of cash flow information:** | | |
| Interest paid | $ 2,977 | $ 3,079 |
| Income taxes paid | $ - | $ 2 |
| | | |
| **Supplemental disclosures of non-cash investing and financing activities:** | | |
| Amounts accrued for capital and patent expenditures | $ 3,204 | $ 835 |

See accompanying notes.

**ISIS PHARMACEUTICALS, INC.**
**NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS**
**September 30, 2014**
**(Unaudited)**

## 1. Basis of Presentation

The unaudited interim condensed consolidated financial statements for the three and nine months ended September 30, 2014 and 2013 have been prepared on the same basis as the audited financial statements for the year ended December 31, 2013. 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, 2013 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, Symphony GenIsis, Inc., which is currently inactive.

## 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 condensed consolidated balance sheet.

*Research and development revenue under collaborative agreements*

Our collaboration agreements typically contain multiple elements, or deliverables, including technology licenses or options to obtain technology licenses, research and development services, and in certain cases manufacturing services. Our collaborations may provide for various types of payments to us including upfront payments, funding of research and development, milestone payments, licensing fees, profit sharing and royalties on product sales. We evaluate the deliverables in our collaboration agreements to determine whether they meet the criteria to be accounted for as separate units of accounting or whether they should be combined with other deliverables and accounted for as a single unit of accounting. When the delivered items in an arrangement have "stand-alone value" to our customer, we account for the deliverables as separate units of accounting and we allocate the consideration to each unit of accounting based on the relative selling price of each deliverable. Delivered items have stand-alone value if they are sold separately by any vendor or the customer could resell the delivered items on a 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.

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

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

We determined that the ISIS-STAT3$_{Rx}$ license had stand-alone value because it is an exclusive license that gives AstraZeneca the right to develop ISIS-STAT3$_{Rx}$ or to sublicense its rights. In addition, ISIS-STAT3$_{Rx}$ is currently in development and it is possible that AstraZeneca or another third party could conduct clinical trials without assistance from us. As a result, we considered the ISIS-STAT3$_{Rx}$ license and the development services for ISIS-STAT3$_{Rx}$ to be separate units of accounting. We recognized the portion of the consideration allocated to the ISIS-STAT3$_{Rx}$ license immediately because we delivered the license and earned the revenue. We are recognizing as revenue the amount allocated to the development services for ISIS-STAT3$_{Rx}$ over the period of time we perform services. The ISIS-AR$_{Rx}$ license is also an exclusive license. At the inception of the agreement, ISIS-AR$_{Rx}$ was in an early stage of research. Therefore, we concluded that our knowledge and expertise with antisense technology was essential for AstraZeneca or another third party to successfully develop ISIS-AR$_{Rx}$. As a result, we determined that the ISIS-AR$_{Rx}$ license did not have stand-alone value and we combined the ISIS-AR$_{Rx}$ license and related research services into one unit of accounting. We recognized revenue for the combined unit of accounting over the period of time we performed services, which ended in the first quarter of 2014. We determined that the options under the research program did not have stand-alone value because AstraZeneca cannot develop or commercialize drugs resulting from the research program until AstraZeneca exercises the respective option or options. As a result, we considered the research options and the related research services as a combined unit of accounting. We are recognizing revenue for the combined unit of accounting over the period of our performance.

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

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

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

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

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

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

Typically, we must estimate our period of performance when the agreements we enter into do not clearly define such information. Our collaborative agreements typically include a research and/or development project plan outlining the activities the agreement requires each party to perform during the collaboration. We estimate the period of time over which we will complete the activities for which we are responsible and use that period of time as our period of performance for purposes of revenue recognition and amortize revenue over such period. 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 these agreements, it may affect the timing and amount of revenue that we recognize in future periods. For example, we adjusted the period of performance on our collaboration with GSK and our ISIS-SMN$_{Rx}$ collaboration with Biogen Idec. As a result of adding two new development candidates, ISIS-HBV$_{Rx}$ and ISIS-GSK4$_{Rx}$, to our collaboration with GSK, our period of performance was extended beyond our initial estimate. Therefore, we extended the amortization period to correspond to the new extended period of performance. Similarly, with our ISIS-SMN$_{Rx}$ collaboration, we extended the amortization period to correspond to the expansion of the Phase 3 study in infants with Spinal Muscular Atrophy, or SMA. Since we extended the amortization period for our GSK collaboration and our ISIS-SMN$_{Rx}$ collaboration, revenue from the amortization of upfront payments for these collaborations will be $3.7 million less in 2014 compared to 2013.

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

- In January 2012, we entered into a collaboration agreement with Biogen Idec to develop and commercialize ISIS-SMN$_{Rx}$ for SMA. As part of the collaboration, we received a $29 million upfront payment and we are responsible for global development of ISIS-SMN$_{Rx}$ through completion of Phase 2/3 clinical trials.

- In June 2012, we entered into a second and separate collaboration agreement with Biogen Idec to develop and commercialize a novel antisense drug targeting DMPK, or dystrophia myotonica-protein kinase. As part of the collaboration, we received a $12 million upfront payment and we are responsible for global development of the drug through the completion of a Phase 2 clinical trial.

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

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

All four of these collaboration agreements give Biogen Idec the option or options to license one or more drugs resulting from the specific collaboration. If Biogen Idec exercises an option, it will pay us a license fee and will assume future development, regulatory and commercialization responsibilities for the licensed drug. We are also eligible to receive milestone payments associated with the research and/or development of the drugs prior to licensing, milestone payments if Biogen Idec achieves pre-specified regulatory milestones, and royalties on any product sales of drugs resulting from these collaborations.

We evaluated all four of the Biogen Idec agreements to determine whether we should account for them as separate agreements. We determined that we should account for the agreements separately because we conducted the negotiations independently of one another, each agreement focuses on different

drugs, there are no interrelated or interdependent 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 Idec cannot pursue the development or commercialization of the drugs resulting from these collaborations until it exercises the respective option or options. As such, for each agreement we considered the deliverables to be a single unit of accounting and we are recognizing the upfront payment for each of the agreements over the respective estimated period of our performance.

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

Prior to the first stage in the life-cycle of our drugs, we perform a significant amount of work using our proprietary antisense technology to design chemical compounds 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 our partner to successfully commercialize our drug. Further, the patent protection afforded our drugs as a result of our initial patent applications and related prosecution activities in the United States and foreign jurisdictions are critical to our partner's ability to sell our drugs without competition from generic drugs. The potential sales volume of an approved drug is dependent on several factors including the size of the patient population, market penetration of the drug, and the price charged for the drug.

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

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

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

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

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

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

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

We assess whether a substantive milestone exists at the inception of our agreements. When a substantive milestone is achieved, we recognize revenue related to the milestone payment. For our existing licensing and collaboration agreements in which we are involved in the discovery and/or development of the related drug or provide the partner with 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 Idec substantive because we are using our antisense drug discovery platform to discover and develop new drugs against targets for neurological diseases. Alternatively, we considered milestones associated with our strategic alliance with Alnylam Pharmaceuticals, Inc. substantive because we provided 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 the estimated period of performance, if any. We consider most milestone payments related to progression of a drug through the development and regulatory stages of its life cycle to be substantive milestones because the level of effort and inherent risk associated with these events is high. Further information about our collaborative arrangements can be found in Note 7, *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 sublicensing revenue from Alnylam related to its collaboration with Genzyme because we have no performance obligations related to Alnylam's relationship with Genzyme and collectability was reasonably assured.

**Cash, cash equivalents and short-term investments**

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

We have equity investments in privately- and publicly-held biotechnology companies that we have received as part of a technology license or collaboration agreement. At September 30, 2014 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 a small company, which we call a satellite company, and realization of our equity position in this company is uncertain. In this circumstance we recorded 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 nine months ended September 30, 2014 and 2013. Total inventory, which consisted of raw materials, was $7.1 million and $8.0 million as of September 30, 2014 and December 31, 2013, 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. For the three and nine months ended September 30, 2014, patent expenses included non-cash charges related to the write-down of our patent costs to their estimated net realizable values of $0.5 million and $0.8 million, respectively, compared to $0.2 million and $0.4 million for the same periods in 2013.

**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.

**Reclassifications**

We have reclassified certain immaterial prior period amounts to conform to the current period presentation. Certain amounts previously reported as research and development revenue have been reclassified to licensing and royalty revenue to conform to the current period presentation.

**Basic and diluted net loss per share**

We compute basic net loss per share by dividing the net loss by the weighted-average number of common shares outstanding during the period. As we incurred a net loss for the three and nine months ended September 30, 2014 and 2013, we did not include dilutive common equivalent shares in the computation of diluted net loss per share because the effect would have been anti-dilutive. Common stock from the following would have had an anti-dilutive effect on net loss per share:

- 2¾ percent convertible senior notes;
- Dilutive stock options; and
- Restricted stock units.

**Consolidation of variable interest entities**

We identify entities as variable interest entities either: (1) that do not have sufficient equity investment at risk to permit the entity to finance its activities without additional subordinated financial support, or (2) in which the equity investors lack an essential characteristic of a controlling financial interest. We perform ongoing qualitative assessments of our variable interest entities to determine whether we have a controlling financial interest in the variable interest entity and therefore are the primary beneficiary. As of September 30, 2014 and December 31, 2013, we had collaborative arrangements with four and five entities, respectively, that we considered to be variable interest entities. We are not the primary beneficiary for any of these entities because we do not have the power to direct the activities that most significantly impact the economic performance of our variable interest entities, the obligation to absorb losses, or the right to receive benefits from our variable interest entities that could potentially be significant to the variable interest entities. As of September

30, 2014, the total carrying value of our investments in variable interest entities was $48.4 million, and was primarily related to our investment in Regulus. Our maximum exposure to loss related to these variable interest entities is limited to the carrying value of our investments.

**Accumulated other comprehensive income**

Accumulated other comprehensive income is comprised of unrealized gains and losses on securities, net of taxes, and adjustments we made to reclassify realized gains and losses on securities from other accumulated comprehensive income to our condensed consolidated statement of operations. The following table summarizes changes in accumulated other comprehensive income for the three and nine months ended September 30, 2014 and 2013 (in thousands):

| | Three Months Ended September 30, | | Nine Months Ended September 30, | |
|---|---|---|---|---|
| | 2014 | 2013 | 2014 | 2013 |
| Beginning balance accumulated other comprehensive income | $ 24,719 | $ 26,986 | $ 21,080 | $ 12,480 |
| Unrealized (losses) gains on securities, net of tax (1) | (6,994) | 2,207 | (3,189) | 17,876 |
| Amounts reclassified from accumulated other comprehensive income (2) | (831) | (172) | (997) | (1,335) |
| Net current period other comprehensive (loss) income | (7,825) | 2,035 | (4,186) | 16,541 |
| Ending balance accumulated other comprehensive income | $ 16,894 | $ 29,021 | $ 16,894 | $ 29,021 |

(1) Other comprehensive (loss) income for the three months ended September 30, 2014 included income tax benefit of $2.5 million, compared to income tax expense of $1.4 million and $11.4 million for the three and nine months ended September 30, 2013, respectively. We recorded no income tax benefit or expense for the nine months ended September 30, 2014.

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

**Convertible debt**

In August 2012, we completed a $201.3 million offering of convertible senior notes, which mature in 2019 and bear interest at 2¾ percent. In September 2012, we used a substantial portion of the net proceeds from the issuance of the 2¾ percent notes to redeem our 2⅝ percent convertible subordinated notes. We account for our 2¾ percent notes by separating the liability and equity components of the instrument in a manner that reflects our nonconvertible debt borrowing rate. As a result, we assigned a value to the debt component of our 2 ¾ percent notes equal to the estimated fair value of similar debt instruments without the conversion feature, which resulted in us recording the debt instrument at a discount. We are amortizing the debt discount over the life of these 2¾ percent notes as additional non-cash interest expense utilizing the effective interest method.

**Segment information**

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

**Stock-based compensation expense**

We measure stock-based compensation expense for equity-classified awards, principally related to stock options, restricted stock units, or RSUs, and stock purchase rights under our Employee Stock Purchase Plan, or ESPP, based on the estimated fair value of the award on the date of grant. We recognize the value of the portion of the award that we ultimately expect to vest as stock-based compensation expense over the requisite service period in our condensed consolidated statements of operations. We reduce stock-based compensation expense for estimated forfeitures at the time of grant and revise in subsequent periods if actual forfeitures differ from those estimates.

We use the Black-Scholes model to estimate the fair value of stock options granted and stock purchase rights under our ESPP. The expected term of stock options granted represents the period of time that we expect them to be outstanding. We estimate the expected term of options granted based on historical exercise patterns. For the nine months ended September 30, 2014 and 2013, we used the following weighted-average assumptions in our Black-Scholes calculations:

*Employee Stock Options:*

| | Nine Months Ended September 30, | |
|---|---|---|
| | 2014 | 2013 |
| Risk-free interest rate | 1.6% | 1.0% |
| Dividend yield | 0.0% | 0.0% |
| Volatility | 50.7% | 51.4% |
| Expected life | 4.6 years | 5.1 years |

*ESPP:*

| | Nine Months Ended September 30, | |
|---|---|---|
| | 2014 | 2013 |
| Risk-free interest rate | 0.1% | 0.1% |
| Dividend yield | 0.0% | 0.0% |
| Volatility | 60.6% | 62.9% |
| Expected life | 6 months | 6 months |

*Board of Director Stock Options:*

| | Nine Months Ended September 30, | |
|---|---|---|
| | 2014 | 2013 |
| Risk-free interest rate | 2.2% | 2.2% |

| | | |
|---|---|---|
| Dividend yield | 0.0% | 0.0% |
| Volatility | 54.2% | 52.7% |
| Expected life | 6.9 years | 7.2 years |

The fair value of RSUs is based on the market price of our common stock on the date of grant. RSUs vest annually over a four year period. The weighted-average grant date fair value of RSUs granted to employees and the Board of Directors for the nine months ended September 30, 2014 was $45.80 and $38.10, respectively.

The following table summarizes stock-based compensation expense for the three and nine months ended September 30, 2014 and 2013 (in thousands), which was allocated as follows:

| | Three Months Ended September 30, | | Nine Months Ended September 30, | |
|---|---|---|---|---|
| | 2014 | 2013 | 2014 | 2013 |
| Research, development and patent expenses | $ 6,606 | $ 2,373 | $ 18,879 | $ 7,171 |
| General and administrative | 1,512 | 439 | 4,015 | 1,147 |
| Total | $ 8,118 | $ 2,812 | $ 22,894 | $ 8,318 |

Non-cash stock-based compensation was $8.1 million and $22.9 million for the three and nine months ended September 30, 2014, respectively, and increased compared to $2.8 million and $8.3 million for the same periods in 2013 primarily due to the increase in our stock price. As of September 30, 2014, total unrecognized estimated non-cash stock-based compensation expense related to non-vested stock options and RSUs was $26.4 million and $11.5 million, respectively. We will adjust total unrecognized compensation cost for future changes in estimated forfeitures. We expect to recognize the cost of non-cash, stock-based compensation expense related to non-vested stock options and RSUs over a weighted average amortization period of 1.3 years and 1.5 years, respectively.

**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 is effective for fiscal years, and interim periods within those years, beginning after December 15, 2016. 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 will adopt this guidance in our fiscal year beginning January 1, 2017. We are currently evaluating an adoption method and the impact this guidance will have on our consolidated financial position, results of operations, cash flows and disclosures, and are currently unable to estimate the impact of this guidance.

In August 2014, the FASB issued accounting guidance on how and when to disclose going-concern uncertainties in the financial statements. This guidance requires 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 those years, 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.

## 3. Investments

As of September 30, 2014, we have invested our excess cash primarily in debt instruments of the U.S. Treasury, financial institutions, corporations, and U.S. government agencies with strong credit ratings and an investment grade rating at or above A-1, P-1 or F-1 by Moody's, Standard & Poor's (S&P) or Fitch, respectively. We have established guidelines relative to diversification and maturities that maintain safety and liquidity. We periodically review and modify these guidelines to maximize trends in yields and interest rates without compromising safety and liquidity.

The following table summarizes the contract maturity of the available-for-sale securities we held as of September 30, 2014:

| | |
|---|---|
| One year or less | 57% |
| After one year but within two years | 32% |
| After two years but within three years | 11% |
| Total | 100% |

As illustrated above, we primarily invest our excess cash in short-term instruments with 89 percent of our available-for-sale securities having a maturity of less than two years.

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

At September 30, 2014, we had an ownership interest of less than 20 percent in one private company and four public companies with which we conduct business. The privately-held company is Atlantic Pharmaceuticals Limited and the publicly-traded companies are Antisense Therapeutics Limited, Achaogen Inc., iCo Therapeutics Inc., and Regulus. We account for equity investments in the privately-held companies under the cost method of accounting and we account for equity investments in the publicly-traded companies at fair value. We record unrealized gains and losses as a separate component of comprehensive income (loss) and include net realized gains and losses in gain (loss) on investments.

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

| September 30, 2014 | Amortized Cost | Unrealized Gains | Unrealized Losses | Other-Than-Temporary Impairment Loss | Estimated Fair Value |
|---|---|---|---|---|---|
| Available-for-sale securities: | | | | | |
| Corporate debt securities(1) | $ 205,973 | $ 153 | $ (67) | $ — | $ 206,059 |
| Debt securities issued by U.S. government agencies (1) | 51,021 | 13 | (35) | — | 50,999 |
| Debt securities issued by the U.S. Treasury | 9,022 | 18 | — | — | 9,040 |
| Debt securities issued by states of the United States and political subdivisions of the states | 38,134 | 19 | (48) | — | 38,105 |

| | | | | | |
|---|---|---|---|---|---|
| Total securities with a maturity of one year or less | 304,150 | 203 | (150) | — | 304,203 |
| Corporate debt securities | 148,079 | 55 | (345) | — | 147,789 |
| Debt securities issued by U.S. government agencies | 55,525 | 5 | (132) | — | 55,398 |
| Debt securities issued by states of the United States and political subdivisions of the states | 26,275 | 41 | (77) | — | 26,239 |
| Total securities with a maturity of more than one year | 229,879 | 101 | (554) | — | 229,426 |
| Total available-for-sale securities | $ 534,029 | $ 304 | $ (704) | $ — | $ 533,629 |

| September 30, 2014 | Cost Basis | Unrealized Gains | Unrealized Losses | Other-Than-Temporary Impairment Loss | Estimated Fair Value |
|---|---|---|---|---|---|
| Equity securities: | | | | | |
| Regulus Therapeutics Inc. | $ 15,316 | $ 32,110 | $ — | $ — | $ 47,426 |
| Securities included in other current assets | 1,269 | 1,021 | — | (1,269) | 1,021 |
| Total equity securities | $ 16,585 | $ 33,131 | $ — | $ (1,269) | $ 48,447 |
| Total available-for-sale and equity securities | $ 550,614 | $ 33,435 | $ (704) | $ (1,269) | $ 582,076 |

| December 31, 2013 | Amortized Cost | Unrealized Gains | Unrealized Losses | Other-Than-Temporary Impairment Loss | Estimated Fair Value |
|---|---|---|---|---|---|
| Available-for-sale securities: | | | | | |
| Corporate debt securities(1) | $ 142,096 | $ 75 | $ (27) | $ — | $ 142,144 |
| Debt securities issued by U.S. government agencies (1) | 23,242 | 22 | (16) | — | 23,248 |
| Debt securities issued by the U.S. Treasury | 6,239 | 6 | — | — | 6,245 |
| Debt securities issued by states of the United States and political subdivisions of the states | 8,082 | 6 | (28) | — | 8,060 |
| Total securities with a maturity of one year or less | 179,659 | 109 | (71) | — | 179,697 |
| Corporate debt securities | 265,969 | 177 | (393) | — | 265,753 |
| Debt securities issued by U.S. government agencies | 41,308 | 3 | (127) | — | 41,184 |
| Debt securities issued by the U.S. Treasury | 9,062 | 21 | — | — | 9,083 |
| Debt securities issued by states of the United States and political subdivisions of the states | 14,186 | 37 | (28) | — | 14,195 |
| Total securities with a maturity of more than one year | 330,525 | 238 | (548) | — | 330,215 |
| Total available-for-sale securities | $ 510,184 | $ 347 | $ (619) | $ — | $ 509,912 |

| December 31, 2013 | Cost Basis | Unrealized Gains | Unrealized Losses | Other-Than-Temporary Impairment Loss | Estimated Fair Value |
|---|---|---|---|---|---|
| Equity securities: | | | | | |
| Regulus Therapeutics Inc. | $ 15,526 | $ 36,570 | $ — | $ — | $ 52,096 |
| Securities included in other current assets | 1,538 | 618 | — | (880) | 1,276 |
| Securities included in deposits and other assets | 625 | — | — | — | 625 |
| Total equity securities | $ 17,689 | $ 37,188 | $ — | $ (880) | $ 53,997 |
| Total available-for-sale and equity securities | $ 527,873 | $ 37,535 | $ (619) | $ (880) | $ 563,909 |

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

Investments we considered to be temporarily impaired at September 30, 2014 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 | 178 | $ 165,321 | $ (397) | $ 9,266 | $ (15) | $ 174,587 | $ (412) |
| Debt securities issued by U.S. government agencies | 10 | 56,358 | (167) | - | - | 56,358 | (167) |
| Debt securities issued by states of the United States and political subdivisions of the states | 19 | 22,661 | (78) | 228 | (47) | 22,889 | (125) |
| Total temporarily impaired securities | 207 | $ 244,340 | $ (642) | $ 9,494 | $ (62) | $ 253,834 | $ (704) |

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 assumptions. Our Level 3 investments include investments in the equity securities of publically held biotechnology companies for which we calculated a lack of marketability discount because there were restrictions on when we could trade the securities. The majority of our securities have been classified as Level 2. We obtain the fair value of our Level 2 investments from our custodian bank or from a professional pricing service. We validate the fair value of our Level 2 investments by understanding the pricing model used by the custodian banks or professional pricing service provider and comparing that fair value to the fair value based on observable market prices. During the nine months ended September 30, 2014, 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 each security is valued with at September 30, 2014 and December 31, 2013 as follows (in thousands):

| | At September 30, 2014 | Quoted Prices in Active Markets (Level 1) | Significant Other Observable Inputs (Level 2) | Significant Unobservable Inputs (Level 3) |
|---|---|---|---|---|
| Cash equivalents | $ 44,551 | $ 44,551 | $ — | $ — |
| Corporate debt securities (1) | 353,848 | — | 353,848 | — |
| Debt securities issued by U.S. government agencies (1) | 106,397 | — | 106,397 | — |
| Debt securities issued by the U.S. Treasury | 9,040 | 9,040 | — | — |
| Debt securities issued by states of the United States and political subdivisions of the states (1) | 64,344 | — | 64,344 | — |
| Investment in Regulus Therapeutics Inc. | 47,426 | 47,426 | — | — |
| Equity securities (2) | 1,021 | 1,021 | — | — |
| Total | $ 626,627 | $ 102,038 | $ 524,589 | $ — |

| | At December 31, 2013 | Quoted Prices in Active Markets (Level 1) | Significant Other Observable Inputs (Level 2) | Significant Unobservable Inputs (Level 3) |
|---|---|---|---|---|
| Cash equivalents | $ 133,233 | $ 133,233 | $ — | $ — |
| Corporate debt securities (1) | 407,897 | — | 407,897 | — |
| Debt securities issued by U.S. government agencies | 64,432 | — | 64,432 | — |
| Debt securities issued by the U.S. Treasury | 15,328 | 15,328 | — | — |
| Debt securities issued by states of the United States and political subdivisions of the states | 22,255 | — | 22,255 | — |
| Investment in Regulus Therapeutics Inc. | 52,096 | 52,096 | — | — |
| Equity securities (2) | 1,276 | 1,276 | — | — |
| Total | $ 696,517 | $ 201,933 | $ 494,584 | $ — |

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

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

When we hold investments in publicly-held biotechnology companies that are subject to trading restrictions, we calculate a lack of marketability discount on the fair value of the investments and categorize these investments as Level 3. 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 ended.

In the first quarter of 2014, Achaogen completed an initial public offering. As a result, we stopped using the cost method of accounting for our equity investment in Achaogen and instead we began accounting for it at fair value. Until September 2014, the fair value of our investment in Achaogen included a lack of marketability discount because there were restrictions on when we could trade the securities. In September 2014, we reclassified our investment in Achaogen to a Level 1 investment because the contractual trading restrictions on the shares we own had ended.

The following is a summary of our investments measured at fair value on a recurring basis using significant unobservable inputs (Level 3) for the nine months ended September 30, 2014 (in thousands):

| | |
|---|---|
| Beginning balance of Level 3 investments | $ - |
| Total gain included in accumulated other comprehensive income (loss) | 1,231 |
| Transfers out of Level 3 investments | (1,231) |
| Ending balance of Level 3 investments | $ - |

**Other Fair Value Disclosures**

Our 2¾ percent convertible notes had a fair value of $490.0 million at September 30, 2014. We determine the fair value of our 2¾ percent convertible notes based on quoted market prices for these notes, which is a Level 2 measurement.

## 5. Concentration of Business Risk

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

| | Three Months Ended September 30, | | Nine Months Ended September 30, | |
|---|---|---|---|---|
| | 2014 | 2013 | 2014 | 2013 |
| Partner A | 72% | 25% | 59% | 16% |
| Partner B | 12% | 48% | 9% | 22% |
| Partner C | 1% | 18% | 15% | 21% |
| Partner D | 0% | 0% | 0% | 31% |

Contract receivables from two significant partners comprised approximately 94 percent of our contract receivables at September 30, 2014. Contract receivables from three significant partners comprised approximately 91 percent of our contract receivables at December 31, 2013.

**6. Income Taxes**

Intraperiod tax allocation rules require us to allocate our provision for income taxes between continuing operations and other categories of earnings, such as other comprehensive income. In periods in which we have a year-to-date pre-tax loss from continuing operations and pre-tax income in other categories of earnings, such as other comprehensive income, we must allocate the tax provision to the other categories of earnings. We then record a related tax benefit in continuing operations. During the nine months ended September 30, 2013, we recorded unrealized gains on our investments in available-for-sale securities in other comprehensive income, net of taxes. As a result, for the nine months ended September 30, 2013, we recorded a $6.4 million tax benefit, compared to income tax expense of $2,000 for the nine months ended September 30, 2014.

## 7. Collaborative Arrangements and Licensing Agreements

**Traditional Pharmaceutical Alliances and Licensing**

*AstraZeneca*

In December 2012, we entered into a global collaboration agreement with AstraZeneca to discover and develop antisense drugs against five cancer targets. As part of the agreement, we granted AstraZeneca an exclusive license to develop and commercialize ISIS-STAT3$_{Rx}$ and ISIS-AR$_{Rx}$ for the treatment of cancer and an option to license up to three cancer drugs under a separate research program. We are eligible to receive milestone payments and license fees from AstraZeneca as programs advance in development. In addition, we are eligible to receive royalties up to the low to mid-teens on any product sales of drugs resulting from this collaboration. Under the terms of the agreement, we received $31 million in upfront and near-term payments comprised of a $25 million upfront payment we received in December 2012 and a $6 million payment we received in June 2013, of which we recognized $11.5 million upon receipt of the payments. We are recognizing the remaining $19.5 million as follows:

- $11.2 million related to the ISIS-AR$_{Rx}$ program, which we amortized through March 2014;
- $7.6 million related to the option to license three drugs under a separate research program, which we are amortizing through December 2016; and
- $0.7 million related to the ISIS-STAT3$_{Rx}$ program, which we are amortizing through November 2014.

Together with AstraZeneca, we are evaluating ISIS-STAT3$_{Rx}$ in patients with advanced cancer. AstraZeneca is conducting a Phase 1b/2a clinical study of ISIS-STAT3$_{Rx}$ in patients with advanced metastatic hepatocellular carcinoma, or HCC. We are also conducting a clinical study evaluating ISIS-STAT3$_{Rx}$ in patients with advanced lymphomas, including patients with diffuse large b-cell lymphoma. We are responsible for completing our clinical study in patients with advanced lymphomas and AstraZeneca is responsible for all other development activities for ISIS-STAT3$_{Rx}$. In October 2014, we and AstraZeneca amended our agreement for ISIS-STAT3$_{Rx}$. Under the amended terms of the agreement, we earned a $7.5 million milestone payment in November 2014, the first of two milestone payments totaling $15 million, from AstraZeneca for the advancement of ISIS-STAT3$_{Rx}$ in patients with advanced cancers. Upon initiation of the Phase 2 study, we will earn the second $7.5 million milestone payment and an additional $10 million milestone payment. In total, we are eligible to receive up to $70 million in milestone payments as ISIS-STAT3$_{Rx}$ advances through clinical development. In addition, we are eligible to earn up to $170 million in regulatory milestone payments plus royalties on the commercial sales of the drug.

In June 2013, we and AstraZeneca added a second development candidate, ISIS-AR$_{Rx}$, to our collaboration. ISIS-AR$_{Rx}$ is an antisense drug we designed to treat patients with prostate cancer by inhibiting the production of the androgen receptor, or AR. From inception through September 2014, we have earned $25 million in milestone payments related to the development of ISIS-AR$_{Rx}$, including a $15 million milestone payment we earned in June 2014 when AstraZeneca initiated a Phase 1 study of ISIS-AR$_{Rx}$.

If AstraZeneca successfully develops ISIS-STAT3$_{Rx}$, ISIS-AR$_{Rx}$, and three drugs under the research program, we could receive substantive milestone payments of more than $865 million, including up to $238 million for the achievement of development milestones and up to $620 million for the achievement of regulatory milestones. 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 research collaboration, and if AstraZeneca exercises its option, it will be responsible for all further development and commercialization of the drug. We received a $750,000 upfront payment, which we are amortizing through December 2015. 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. 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 royalties up to the low teens on sales from any product that AstraZeneca successfully commercializes under this collaboration program.

Our agreement with AstraZeneca 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:

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

During the three and nine months ended September 30, 2014, we earned revenue of $627,000 and $19.7 million, respectively, from our relationship with AstraZeneca which represented one percent and 15 percent, respectively, of our total revenue for those periods. In comparison, we earned revenue of $4.2 million and $22.0 million for the same periods in 2013. Our balance sheet at September 30, 2014 included deferred revenue of $4.8 million related to our relationship with AstraZeneca.

*Biogen Idec*

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

*ISIS-SMN$_{Rx}$*

In January 2012, we entered into a global collaboration agreement with Biogen Idec to develop and commercialize ISIS-SMN$_{Rx}$ for the treatment of SMA. We received an upfront payment of $29 million, which we are amortizing through February 2017. We are eligible to receive a license fee, milestone payments and royalties up to the mid-teens on any product sales of ISIS-SMN$_{Rx}$. Biogen Idec has the option to license ISIS-SMN$_{Rx}$ until completion of the first successful Phase 2/3 study or the completion of two Phase 2/3 studies. If Biogen Idec exercises its option, it will pay us a license fee and will assume global development, regulatory and commercialization responsibilities. In 2014, we and Biogen Idec amended our original agreement to reflect changes made to the clinical development plan for ISIS-SMN$_{Rx}$. As a result, we and Biogen Idec agreed to increase the payments that we are eligible to receive under this collaboration by approximately $57 million.

In the third quarter of 2014, we initiated the Phase 3 study evaluating ISIS-SMN$_{Rx}$ in infants with SMA, for which we earned an $18 million milestone payment when we dosed the first patient. In addition, we are evaluating ISIS-SMN$_{Rx}$ in a Phase 2 open-label, multiple-dose, dose-escalation study in children with SMA and a Phase 2 open-label, multiple-dose, dose-escalation pilot study in infants with SMA. From inception through September 2014, we have earned $37.3 million in payments for advancing ISIS-SMN$_{Rx}$, including $11.3 million in payments we earned related to the amendments made to the clinical development plan for ISIS-SMN$_{Rx.}$ Accounting rules require us to amortize the $11.3 million we received related to the amendments of the clinical development plan for ISIS-SMN$_{Rx}$ over our estimated period of performance, which is as follows:

- $3.8 million related to the Phase 2 studies in children and infants with SMA, which we amortized through July 2014; and
- $7.5 million related to an open-label extension study in children with SMA, which we are amortizing through December 2014.

Under the terms of the amended agreement, we are eligible to receive up to $327.2 million in a license fee and payments, including $102.2 million in substantive milestone and other payments associated with the clinical development of ISIS-SMN$_{Rx}$ prior to licensing and $150 million in substantive milestone payments if Biogen Idec achieves pre-specified regulatory milestones. We will earn the next milestone payment of $27 million if we dose the first patient in the Phase 3 study of ISIS-SMN$_{Rx}$ in children with SMA, which is designed to support marketing registration for ISIS-SMN$_{Rx}$ in the United States and Europe.

*ISIS-DMPK$_{Rx}$*

In June 2012, we and Biogen Idec entered into a second and separate collaboration and license agreement to develop and commercialize a novel antisense drug targeting DMPK for the treatment of myotonic dystrophy type 1, or DM1, ISIS-DMPK$_{Rx}$. We are responsible for global development of the drug through the completion of the first Phase 2 clinical trial. Biogen Idec has the option to license the drug through the completion of the first Phase 2 trial. Under the terms of the agreement, we received an upfront payment of $12 million, which we are amortizing through June 2017. Over the term of the collaboration, we are eligible to receive up to $259 million in a license fee and substantive milestone payments. From inception through September 2014, we have earned $24 million in substantive milestone payments associated with the clinical development of ISIS-DMPK$_{Rx}$, including a $14 million milestone payment we earned in June 2014 when we initiated a Phase 1 study for ISIS-DMPK$_{Rx}$. We are eligible to receive up to another $35 million in milestone payments associated with the development of ISIS-DMPK$_{Rx}$ prior to licensing. We are also eligible to receive up to $130 million in milestone payments if Biogen Idec achieves pre-specified regulatory milestones. In addition, we are eligible to receive royalties up to the mid-teens on any product sales of the drug. We will earn the next milestone payment of $35 million if we initiate a Phase 2 study for ISIS-DMPK$_{Rx}$.

*Neurology*

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

*Strategic Neurology*

In September 2013, we and Biogen Idec entered into a fourth and separate collaboration, which is a long-term strategic relationship focused on applying antisense technology to advance the treatment of neurological diseases. As part of the collaboration, Biogen Idec 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 six years, and may be extended for any drug development programs being pursued under the collaboration. Under the terms of the agreement, we received an upfront payment of $100 million and are eligible to receive milestone payments, license fees and royalty payments for all drugs developed through this collaboration, with the specific amounts dependent upon the modality of the molecule advanced by Biogen Idec. If we have a change of control during the first six years of the collaboration, we may be required to refund Biogen Idec a portion of the $100 million upfront payment, with the amount of the potential refund decreasing ratably as we progress through the initial six year term of the collaboration. We 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 Idec 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. We will usually be responsible for drug discovery and early development of antisense drugs and Biogen Idec will have the option to license antisense drugs after Phase 2 proof of concept. Biogen Idec will then be responsible for later phase development and commercialization of the licensed drug. In addition, we are eligible to receive royalties up to the mid-teens on any product sales of antisense drugs developed under this collaboration. If other modalities, such as small molecules or monoclonal antibodies, are chosen, 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. Biogen Idec will be responsible for all of the drug discovery and development activities for drugs using other modalities. In addition, we are eligible to receive single-digit royalties on any product sales of drugs using non-antisense modalities developed under this collaboration. In June 2014, we earned a $10 million milestone payment when Biogen Idec chose the first target to advance under this collaboration and in November 2014 we earned an additional $10 million milestone payment when we initiated an IND-enabling toxicology study for another 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 Idec will continue until the earlier of the date all of Biogen Idec's options to obtain the exclusive licenses under the applicable agreement expire unexercised or, if Biogen Idec 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 Idec 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 Idec 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 Idec may terminate the affected program by providing written notice to the other party; and
- Either we or Biogen Idec may terminate any program by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement with respect to the affected program, or the entire agreement if the other party becomes insolvent.

During the three and nine months ended September 30, 2014, we earned revenue of $31.7 million and $76.4 million, respectively, from our relationship with Biogen Idec, which represented 72 percent and 59 percent of our total revenue for those periods. In comparison, we earned revenue of $5.9 million and $17.1 million for the same periods in 2013. Our balance sheet at September 30, 2014 included deferred revenue of $127.4 million related to our relationship with Biogen Idec.

*GSK*

In March 2010, we entered into a strategic alliance with GSK, for up to six programs, 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. This alliance allows us to control and facilitate development of drugs while still being eligible to receive milestone payments as we advance these drugs in clinical development. Our strategic alliance currently includes five active programs. Under the terms of the agreement, we received a $35 million upfront payment and in May 2011 we received a $3 million payment when GSK expanded the collaboration. In addition, we are eligible to receive on average up to $20 million in milestone payments through Phase 2 proof-of-concept for each program, except for ISIS-$TTR_{Rx}$ and the fifth target, which we describe below. 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.

In October 2012, we and GSK amended the original agreement to reflect an accelerated clinical development plan for ISIS-$TTR_{Rx}$. Under the amended terms of the agreement, we received a $2.5 million upfront payment in December 2012. From inception through September 2014, we have received $27 million, primarily in milestone payments, from GSK related to the development of ISIS-$TTR_{Rx}$, not including an $18 million milestone payment we earned in October 2014 related to the advancement of the Phase 2/3 study of ISIS-$TTR_{Rx}$ in patients with familial amyloid polyneuropathy. We are also eligible to earn an additional $25 million in pre-licensing milestone payments associated with the ISIS-$TTR_{Rx}$ Phase 2/3 study. In addition, under the amended agreement, we and GSK increased the regulatory and commercial milestone payments we can earn should ISIS-$TTR_{Rx}$ receive marketing approval and meet pre-agreed sales targets.

In September 2013, we designated ISIS-HBV$_{Rx}$, formerly ISIS-GSK3$_{Rx}$, as a development candidate under our collaboration with GSK. ISIS-HBV$_{Rx}$ is an antisense drug designed to reduce the production of viral proteins associated with hepatitis B virus, or HBV, infection and replication. In June 2014, we amended our agreement to modify the development plans for ISIS-HBV$_{Rx}$. As a result, we received a $1 million payment. From inception through September 2014, we have earned $10 million in substantive milestone payments associated with advancing the ISIS-HBV$_{Rx}$ program.

From inception through September 2014, we have earned $6.5 million in milestone payments for advancing ISIS-GSK4$_{Rx}$, including a $1.5 million milestone payment we earned in September 2014 when we initiated an IND-enabling toxicology study of ISIS-GSK4$_{Rx}$. In addition, in November 2014, we earned a $5 million milestone payment when we designated ISIS-GSK5$_{Rx}$ as a development candidate. ISIS-GSK4$_{Rx}$ and ISIS-GSK5$_{Rx}$ are antisense drugs we designed to treat undisclosed ocular diseases. We and GSK amended our agreement to modify the development plans for ISIS-GSK4$_{Rx}$ and ISIS-GSK5$_{Rx}$ in April 2014. From inception through November 2014, we have earned $11.5 million in milestone payments associated with advancing ISIS-GSK4$_{Rx}$ and ISIS-GSK5$_{Rx}$.

Under our agreement, if GSK successfully develops all five programs for one or more indications and achieves pre-agreed sales targets, we could receive license fees and substantive milestone payments of more than $1.2 billion, including up to $147.5 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. We will earn the next $1.0 million milestone payment if we further advance the ISIS-HBV$_{Rx}$ program. In addition, we are eligible to receive 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 all of GSK's options to obtain the exclusive licenses under the agreement expire unexercised or, if GSK exercises its option, until the expiration of all payment obligations under the agreement. In addition, the agreement, or any program under the agreement, may terminate early under the following situations:

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

During the three and nine months ended September 30, 2014, we earned revenue of $5.1 million and $11.9 million, respectively, from our relationship with GSK, which represented 12 percent and nine percent, respectively, of our total revenue for those periods. In comparison, we earned revenue of $11.3 million and $23.5 million for the same periods in 2013. Our balance sheet at September 30, 2014 included deferred revenue of $11.1 million related to our relationship with GSK, $9 million of which is related to the upfront and other payments associated with our collaboration with GSK that we are amortizing through our estimated period of performance of September 2015.

*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. We are also working collaboratively with Roche on the discovery of an antisense drug utilizing Roche's "brain shuttle" program. If Roche exercises its option, it will be responsible for global development, regulatory and commercialization activities for any drug arising out of the collaboration. 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 milestones. 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. We will earn the next milestone payment of $22 million if we initiate a Phase 1 trial for a drug targeting HTT protein.

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

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

During the three and nine months ended September 30, 2014, we earned revenue of $2.3 million and $6.7 million, respectively, from our relationship with Roche. In comparison, we earned revenue of $1.9 million and $3.2 million for the three and nine months ended September 30, 2013, respectively. Our balance sheet at September 30, 2014 included deferred revenue of $19.0 million related to our relationship with Roche.

**Satellite Company Collaborations**

*Achaogen, Inc.*

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

In connection with the license, Achaogen issued to us $1.5 million of Achaogen Series A Preferred Stock. Since early 2009, we have earned $7 million in milestone payments from Achaogen, including $4 million we earned in September 2014 when Achaogen initiated a Phase 3 study of plazomicin in patients with serious multi-drug resistant, gram-negative bacterial infections. Assuming Achaogen successfully develops and commercializes two drugs under our agreement, we will receive payments totaling up to $42.3 million for the achievement of key clinical, regulatory and sales events. We will earn the next payment of $7.5 million if Achaogen obtains regulatory approval for plazomicin in a major market. We are also eligible to receive royalties on sales of drugs resulting from the program. Achaogen is solely responsible for the continued development of plazomicin.

In March 2014, Achaogen completed an initial public offering. Upon the close of the offering, our investment in Achaogen's preferred stock converted into approximately 148,000 shares of common stock. As of September 30, 2014, the fair value of our investment in Achaogen was $1.0 million. At September 30, 2014 and December 31, 2013, we owned less than 10 percent of Achaogen's equity.

*Alnylam Pharmaceuticals, Inc.*

In March 2004, we entered into a strategic alliance with Alnylam to develop and commercialize RNA interference therapeutics. Under the terms of the agreement, we exclusively licensed to Alnylam our patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a $5 million technology access fee, participation in fees from Alnylam's partnering programs, as well as future milestone and royalty payments from Alnylam. In August 2012, we expanded the license to include using the double-stranded RNAi technology for agricultural products. For each drug Alnylam develops under this alliance, we may receive up to $3.4 million in substantive milestone payments, including up to $1.1 million for the achievement of development milestones and $2.3 million for regulatory milestones. In 2013, we earned a $750,000 milestone payment when Alnylam initiated a Phase 3 study for a drug targeting transthyretin amyloidosis, or TTR. We will earn the next milestone payment of $375,000 if Alnylam initiates a Phase 1 study for a drug in Alnylam's pipeline. We retained rights to a limited number of double-stranded RNAi therapeutic targets and all rights to single-stranded RNAi, or ssRNAi, therapeutics.

In turn, Alnylam nonexclusively licensed to us its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry to research, develop and commercialize ssRNAi therapeutics and to research double-stranded RNAi compounds. We also received a license to develop and commercialize double-stranded RNAi drugs targeting a limited number of therapeutic targets on a nonexclusive basis. If we develop or commercialize an RNAi-based drug using Alnylam's technology, we will pay Alnylam milestone payments and royalties. For each drug, the potential milestone payments to Alnylam total $3.4 million, which we will pay if we achieve specified development and regulatory events. To date, we do not have an RNAi-based drug in clinical development. Our Alnylam alliance provides us with an opportunity to realize substantial value from our pioneering work in antisense mechanisms and oligonucleotide chemistry and is an example of our strategy to participate in all areas of RNA-targeting drug discovery.

We have the potential to earn sublicense revenue and a portion of milestone payments and royalty payments that Alnylam receives from licenses of our technology it grants to its partners. Through September 2014, we have earned a total of $48.2 million from Alnylam resulting from licenses of our technology for the development of RNAi technology that we granted to Alnylam and Alnylam has granted to its partners, including $7.7 million we earned in the first quarter of 2014 related to Alnylam's collaboration with Genzyme. During the nine months ended September 30, 2014 and 2013, we earned revenue of $7.7 million and $0.4 million, respectively, from our relationship with Alnylam.

**8. Subsequent Event**

In November 2014, Regulus completed a public offering. As part of the offering, we sold 1,279,411 shares of Regulus' common stock for total proceeds of $20.4 million, resulting in a $17.8 million gain, which we will recognize in the fourth quarter of 2014. As part of the public offering, Regulus' directors, executive management team, and some of its stockholders, including us, have agreed that until January 27, 2015, subject to specified exceptions, not to offer, sell, contract to sell, pledge or otherwise dispose of, directly or indirectly, any shares of Regulus' common stock or securities convertible into or exchangeable or exercisable for any shares 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, Symphony GenIsis, Inc., which is currently inactive.*

### Forward-Looking Statements

In addition to historical information contained in this Report on Form 10-Q, this Report includes forward-looking statements regarding our business, the therapeutic and commercial potential of our technologies and products in development, and the financial position of Isis Pharmaceuticals, Inc. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning our programs are described in additional detail in our Annual Report on Form 10-K for the year ended December 31, 2013, which is on file with the U.S. Securities and Exchange Commission, and those identified within this Item in the section entitled "Risk Factors" beginning on page 23 of this Report.

### Overview

We are the leading company in antisense drug discovery and development, exploiting a proven novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs. Our strategy is to do what we do best—to discover and develop unique antisense drugs. The efficiency and broad applicability of our drug discovery platform allows us to discover and develop antisense drugs to treat a wide range of diseases, including severe and rare, cardiovascular, neurologic and metabolic diseases 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 flagship product, KYNAMRO (mipomersen sodium) injection, is on the market in the United States for patients with homozygous familial hypercholesterolemia, or HoFH. Patients with HoFH are at high cardiovascular risk and cannot reduce their low-density lipoprotein cholesterol, or LDL-C, sufficiently with currently available lipid-lowering therapies. In January 2013, the U.S. Food and Drug Administration, or 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 and Peru, and is pursuing marketing approval in multiple additional markets. Genzyme has expertise in successfully marketing drugs in the United States and internationally for severe and rare diseases and is using this expertise to reach patients with HoFH who are in desperate need of new treatment options. Genzyme is concentrating marketing and sales efforts on lipid specialists, and physicians who refer HoFH patients to these specialists, to reach patients with HoFH in the United States and other countries.

We have created a mature and broad pipeline that goes well beyond KYNAMRO. We have a pipeline of 34 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. One of these drugs, ISIS-APOCIII$_{Rx}$, is a drug we designed to treat patients with severely high triglyceride levels, including patients with a severe and rare genetic condition called familial chylomicronemia syndrome, or FCS. We have completed a broad Phase 2 program demonstrating that ISIS-APOCIII$_{Rx}$ significantly reduced triglyceride and apolipoprotein C-III, or apoC-III, levels in patients when evaluated as a single agent and in combination with fibrates. We initiated a Phase 3 program in the third quarter of 2014 to support a potential 2016 regulatory filing for marketing approval for ISIS-APOCIII$_{Rx}$. In addition to ISIS-APOCIII$_{Rx}$, we are also evaluating ISIS-TTR$_{Rx}$ and ISIS-SMN$_{Rx}$ in Phase 3 studies. We designed these drugs to treat patients with severe and rare diseases, such as transthyretin amyloidosis, or TTR, and spinal muscular atrophy, or SMA, who have very limited therapeutic options. Because of the significant unmet medical need and the severity of these diseases, new therapeutic approaches could warrant an accelerated path to market. ISIS-TTR$_{Rx}$ is already in Phase 3 development, and we initiated a Phase 3 program for ISIS-SMN$_{Rx}$ in July 2014. We believe that all three 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. We reported Phase 2 data for ISIS-GCGR$_{Rx}$ and ISIS-FXI$_{Rx}$ in May 2014 and we plan to report data for ISIS-PTP1B$_{Rx}$ and ISIS-GCCR$_{Rx}$, in late 2014 or early 2015.

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 an optimal time to maximize the near- and long-term value for each drug. In this way, we can expand our and our partners' pipelines with antisense drugs that we design to address significant medical needs while remaining small and focused. We form traditional partnering alliances that enable us to discover and conduct early development of new drugs, outlicense our drugs to partners, such as Genzyme, and build a base of license fees, milestone payments, profit share and royalty income. We also form preferred partner transactions that provide us with a vested partner, such as AstraZeneca, Biogen Idec, GSK, and Roche, early in the development of a drug. Typically, the drugs we partner early in development are in therapeutic areas of high risk, like severe neurological diseases, or in areas where Phase 2 results would likely not provide a significant increase in value, like cancer. These preferred partner transactions allow us to develop select drugs that could have significant commercial potential with a knowledgeable and committed partner with the financial resources to fund later-stage clinical studies and expertise to complement our own development efforts. We benefit from this strategy because it allows us to expand and broaden our drug discovery efforts to new disease targets. For example, through our broad strategic partnership with Biogen Idec, we are capitalizing on Biogen Idec's extensive resources and expertise in neurological diseases to create a franchise of novel treatments for neurological disorders. Similar to our other partnerships, with our preferred partner transactions we benefit financially from upfront payments, milestone payments, licensing fees and royalties.

We also work with a consortium of smaller companies that can exploit our drugs and technology. We call these smaller companies our 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. We also maintain our broad ribonucleic acid, or RNA, technology leadership through collaborations with satellite companies. All of these different types of relationships are part of our partnership strategy, which allow us 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.

The broad applicability of our drug discovery technology and the clinical successes of the drugs in our pipeline continue to create new partnering opportunities. Since January 2012, we have initiated six new partnerships that involve antisense drugs for the treatment of neurological diseases or cancer, including four strategic alliances with Biogen Idec to discover and develop antisense drugs for the treatment of neurologic diseases, a strategic alliance with AstraZeneca to discover and develop antisense drugs to treat cancer and a strategic alliance with Roche to discover and develop antisense drugs to treat Huntington's disease. We have received more than $230 million in upfront payments and have the potential to earn nearly $6 billion in future milestone payments and licensing fees from these partnerships. In addition, we have the potential to earn nearly $3 billion in future milestone payments and licensing fees from our other partnered programs. 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. Since 2007, our partnerships have generated an aggregate of more than $1.2 billion in payments from upfront and licensing fees, equity purchase payments, milestone payments and research and development funding.

As an innovator in RNA-targeting drug discovery and development, we design and execute our patent strategy to provide us with extensive protection for our drugs and our technology. With our ongoing research and development, we continue to add to our substantial patent estate. Our patents not only protect our key assets—our technology and our drugs—they also form the basis for lucrative licensing and partnering arrangements. To date, we have generated nearly $420 million from our intellectual property sale and licensing program that helps support our internal drug discovery and development programs.

**Recent Events**

***Corporate and Drug Development Highlights from the Third Quarter and Early Fourth Quarter***

● We reported positive clinical results for ISIS-SMN$_{Rx}$ from two open-label Phase 2 studies in infants and children with SMA. These data were presented at the World Muscle Society Congress.

- We reported that the median event-free age of infants with SMA on September 2, 2014 compared favorably to that of infants with SMA in the Pediatric Neuromuscular Clinical Research Network for Spinal Muscular Atrophy natural history study.
- We reported that time and dose-dependent increases in muscle function scores were observed in both infants and children with SMA.
- We presented clinical data showing that ISIS-SMN$_{Rx}$ is distributed throughout the spinal cord and neurons with greater amounts of full-length SMN2 messenger RNA, or mRNA, and SMN protein in tissues from ISIS-SMN$_{Rx}$-treated infants compared to the amounts of full-length SMN2 mRNA and SMN protein in the tissues analyzed from untreated SMA infants.

● Our collaborators reported positive clinical results from three drugs in our lipid franchise. These data were presented at the 2014 European Society of Cardiology Congress.

- Dr. John Kastelein, M.D., Ph.D. presented data from a retrospective analysis of 104 patients with familial hypercholesterolemia treated for one year with KYNAMRO injection in the long-term extension study showing that patients treated with KYNAMRO experienced a reduction in Major Adverse Cardiovascular Events, or MACE, from 25.72/1000 months (in the two years prior to KYNAMRO treatment) to 4.85/1000 months.
- Dr. John Kastelein provided an overview of the Phase 2 program for ISIS-APOCIII$_{Rx}$ in which treatment with ISIS-APOCIII$_{Rx}$ produced consistent, robust and statistically significant reductions in triglycerides, apoC-III and non-HDL-Cholesterol and increases in HDL-Cholesterol in all patient populations evaluated.
- Dr. Sotirios Tsimikas, M.D. presented data from the Phase 1 study in which treatment with ISIS-APO(a)$_{Rx}$ produced dose-dependent and significant reductions in Lp(a) levels in healthy volunteers.

● Our partner, Regulus, reported positive interim results on RG-101, an anti-miR drug in development to treat patients with hepatitis C virus.

- Regulus reported a single dose of RG-101 demonstrated a substantial mean reduction in viral load in patients with varied hepatitis C virus genotypes and treatment history.

● Together with our partners, we continued to advance our pipeline of drugs.

- We initiated ENDEAR, the Phase 3 study evaluating ISIS-SMN$_{Rx}$ in infants with SMA.
- We initiated APPROACH, the Phase 3 study evaluating ISIS-APOCIII$_{Rx}$ in patients with familial chylomicronemia syndrome.
- Achaogen initiated a Phase 3 study of plazomicin in patients with serious multi-drug resistant, gram-negative bacterial infections.
- We added a new drug, ISIS-BIIB3$_{Rx}$, to our pipeline. ISIS-BIIB3$_{Rx}$ is part of our strategic neurology alliance with Biogen Idec and is in development to treat an undisclosed neurodegenerative disease.
- We added a new drug, ISIS-GSK5$_{Rx}$, to our pipeline. ISIS-GSK5$_{Rx}$ is part of our alliance with GSK and is in development to treat an undisclosed ocular disease.
- We added a new drug, ISIS-HTT$_{Rx}$, to our pipeline. ISIS-HTT$_{Rx}$ is part of our alliance with Roche and is in development to treat patients with Huntington's Disease.

**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;
- Assessing the recoverability of long-lived assets, including property and equipment, intellectual property and licensed technology;
- Determining the appropriate cost estimates for unbilled preclinical studies and clinical development activities;
- Estimating our net deferred income tax asset valuation allowance;
- Determining the fair value of convertible debt without the conversion feature;

There have been no material changes to our critical accounting policies and estimates from the information provided in Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations", included in our Annual Report on Form 10-K for the year ended December 31, 2013.

**Results of Operations**

**Revenue**

Total revenue for the three and nine months ended September 30, 2014 was $44.1 million and $129.3 million, respectively, was significantly higher than revenue for the same periods in 2013 of $23.6 million and $105.0 million, respectively. 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. Our revenue from milestone payments increased to $66.5 million in 2014 compared to $57 million in 2013, primarily because of payments we have earned as we have advanced the drugs in our pipeline. In addition, our revenue from the amortization of upfront fees also increased to $46.0 million compared to $29.8 million in 2013 primarily due to the amortization of the $100 million upfront fee related to the strategic neurology partnership we entered into with Biogen Idec in September 2013.

*Research and Development Revenue Under Collaborative Agreements*

Research and development revenue under collaborative agreements for the three and nine months ended September 30, 2014 was $43.8 million and $120.0 million, respectively, compared to $23.3 million and $102.5 million for the same periods in 2013. Our revenue from the amortization of payments from our partners was $46.0 million for the nine months ended September 30, 2014, compared to $29.8 million for the same period in 2013, and increased primarily due to the amortization of the $100 million upfront fee related to the strategic neurology partnership we entered into with Biogen Idec in September 2013. We also earned $66.5 million in milestone payments for the nine months ended September 30, 2014. The revenue from milestone payments in 2014 was comprised of:

- $43 million from Biogen Idec related to advancing ISIS-SMN$_{Rx}$, initiating a Phase 1 study for ISIS-DMPK$_{Rx}$, and validating an undisclosed target to treat a neurological disorder;
- $15 million from AstraZeneca related to the initiation of a Phase 1 clinical study of ISIS-AR$_{Rx}$;
- $4.5 million from GSK related to advancing the Phase 2/3 study of ISIS-TTR$_{Rx}$ and advancing ISIS-GSK4$_{Rx}$; and
- $4 million from Achaogen when Achaogen initiated a Phase 3 study of plazomicin.

Already in the fourth quarter, we earned $23 million in milestone payments from GSK for advancing ISIS-TTR$_{Rx}$ and for designating ISIS-GSK5$_{Rx}$ as a development candidate. We also earned a $10 million milestone payment from Biogen Idec and a $7.5 million milestone payment from AstraZeneca as the partnered programs in these alliances advanced. We will recognize these milestone payments as revenue in our fourth quarter 2014 financial results.

*Licensing and Royalty Revenue*

Our revenue from licensing activities and royalties for the three and nine months ended September 30, 2014 was $0.3 million and $9.3 million, respectively, compared to $0.3 million and $2.5 million for the same period in 2013. The increase in the first nine months of 2014 was primarily a result of the $7.7 million in sublicensing revenue we earned from Alnylam related to its collaboration with Genzyme.

**Operating Expenses**

Operating expenses for the three and nine months ended September 30, 2014 were $65.6 million and $187.1 million, respectively, compared to $49.1 million and $136.8 million for the same periods in 2013 due to higher development costs associated with our maturing pipeline of drugs, including costs associated with our Phase 3 programs for ISIS-TTR$_{Rx}$, ISIS-SMN$_{Rx}$, and ISIS-APOCIII$_{Rx}$. As drugs move forward to more advanced stages of development, including into larger, longer clinical studies, the costs of development increase. In addition to the Phase 3 programs we are conducting, we initiated Phase 2 studies for several drugs in our pipeline in the second half of 2013, which are ongoing, and advanced several drugs into clinical development in the third quarter of 2014.

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 2014 compared to 2013 primarily due to the increase in our stock price.

***Research, Development and Patent Expenses***

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

The following table sets forth information on research, development and patent expenses (in thousands):

| | Three Months Ended September 30, | | Nine Months Ended September 30, | |
|---|---|---|---|---|
| | 2014 | 2013 | 2014 | 2013 |
| Research, development and patent expenses | $ 54,480 | $ 43,287 | $ 154,919 | $ 119,432 |
| Non-cash compensation expense related to equity awards | 6,606 | 2,373 | 18,879 | 7,171 |
| Total research, development and patent expenses | $ 61,086 | $ 45,660 | $ 173,798 | $ 126,603 |

For the three and nine months ended September 30, 2014, our total research, development and patent expenses were $54.5 million and $154.9 million, respectively, and were higher compared to $43.3 million and $119.4 million for the same periods in 2013 primarily due to the progression of numerous drugs in our pipeline into later stage clinical trials. As drugs move forward to more advanced stages of development, including into larger, longer

clinical studies, the costs of development increase. For example, we initiated Phase 2 studies for several of the drugs in our pipeline in the second half of 2013, which are ongoing, and we advanced several drugs into clinical development in the third quarter of 2014. In addition, we incurred more costs in 2014 compared to 2013 associated with the clinical studies of ISIS-$TTR_{Rx}$, ISIS-$SMN_{Rx}$, and ISIS-$APOCIII_{Rx}$, as we continued to advance those drugs. 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 September 30, | | Nine Months Ended September 30, | |
|---|---|---|---|---|
| | 2014 | 2013 | 2014 | 2013 |
| Antisense drug discovery expenses | $ 11,151 | $ 9,503 | $ 31,006 | $ 29,754 |
| Non-cash compensation expense related to equity awards | 1,829 | 667 | 5,359 | 2,118 |
| Total antisense drug discovery | $ 12,980 | $ 10,170 | $ 36,365 | $ 31,872 |

Antisense drug discovery costs for the three and nine months ended September 30, 2014 were $11.2 million and $31.0 million, respectively, and were slightly higher as expected compared to $9.5 million and $29.8 million for the same periods in 2013 because we were conducting more research studies in 2014 to support our partnerships. All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Development

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

| | Three Months Ended September 30, | | Nine Months Ended September 30, | |
|---|---|---|---|---|
| | 2014 | 2013 | 2014 | 2013 |
| KYNAMRO | $ 1,411 | $ 2,913 | $ 3,875 | $ 6,504 |
| ISIS-$TTR_{Rx}$ | 2,949 | 1,534 | 7,981 | 3,519 |
| ISIS-$SMN_{Rx}$ | 5,480 | 2,115 | 13,895 | 6,278 |
| ISIS-$APOCIII_{Rx}$ | 3,893 | 1,825 | 8,121 | 5,472 |
| Other antisense development products | 14,548 | 11,513 | 44,410 | 27,291 |
| Development overhead costs | 2,757 | 1,982 | 9,300 | 5,542 |
| Non-cash compensation expense related to equity awards | 2,536 | 741 | 6,938 | 2,317 |
| Total antisense drug development | $ 33,574 | $ 22,623 | $ 94,520 | $ 56,923 |

Antisense drug development expenses were $31.0 million and $87.6 million, respectively, for the three and nine months ended September 30, 2014, compared to $21.9 million and $54.6 million for the same periods in 2013. Expenses in the first nine months of 2014 were higher compared to the same period in 2013 primarily due to an increase in development costs associated with the progression of numerous drugs in our pipeline into later stage clinical trials. As drugs move forward to more advanced stages of development, including into larger, longer clinical studies the costs of development increase. For example, in the second half of 2013, we initiated Phase 2 studies for several of the drugs in our pipeline, which are ongoing, and we advanced several drugs into clinical development. In addition, we incurred more costs in 2014 compared to 2013 associated with the clinical studies of ISIS-$TTR_{Rx}$, ISIS-$SMN_{Rx}$, and ISIS-$APOCIII_{Rx}$, as we continued to advance those drugs. We began separately disclosing ISIS-$SMN_{Rx}$ and ISIS-$APOCIII_{Rx}$, in the table above in the third quarter of 2014 because we initiated Phase 3 trials for these drugs during the period. Previously, these amounts were included in other antisense development products. All amounts exclude non-cash compensation expense related to equity awards.

We may conduct multiple clinical trials on a drug candidate, including multiple clinical trials for the various indications we may be studying. Furthermore, as we obtain results from trials we may elect to discontinue clinical trials for certain drug candidates in certain indications in order to focus our resources on more promising drug candidates or indications. Our Phase 1 and Phase 2 programs are clinical research programs that fuel our Phase 3 pipeline. When our products are in Phase 1 or Phase 2 clinical trials, they are in a dynamic state in which we continually adjust the development strategy for each product. Although we may characterize a product as "in Phase 1" or "in Phase 2," it does not mean that we are conducting a single, well-defined study with dedicated resources. Instead, we allocate our internal resources on a shared basis across numerous products based on each product's particular needs at that time. This means we are constantly shifting resources among products. Therefore, what we spend on each product during a particular period is usually a function of what is required to keep the products progressing in clinical development, not what products we think are most important. For example, the number of people required to start a new study is large, the number of people required to keep a study going is modest and the number of people required to finish a study is large. However, such fluctuations are not indicative of a shift in our emphasis from one product to another and cannot be used to accurately predict future costs for each product. And, because we always have numerous 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 discovery and antisense drug development, including the analytical testing to satisfy good laboratory and good manufacturing practices requirements.

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

| | Three Months Ended September | Nine Months Ended September |
|---|---|---|

| | 30, | | 30, | |
|---|---|---|---|---|
| | 2014 | 2013 | 2014 | 2013 |
| Manufacturing and operations | $ 5,562 | $ 5,454 | $ 16,554 | $ 14,029 |
| Non-cash compensation expense related to equity awards | 756 | 306 | 2,205 | 965 |
| Total manufacturing and operations | $ 6,318 | $ 5,760 | $ 18,759 | $ 14,994 |

Manufacturing and operations expenses were $5.6 million and $16.6 million, respectively, for the three and nine months ended September 30, 2014, compared to $5.5 million and $14.0 million for the same periods in 2013. Manufacturing increased for the first nine months of 2014 primarily because we manufactured more drug product to support our drug development activities, including drug product to support the Phase 3 trial for ISIS-APOCIII$_{Rx}$. All amounts exclude non-cash compensation expense related to equity awards.

R&D Support

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

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

| | Three Months Ended September 30, | | Nine Months Ended September 30, | |
|---|---|---|---|---|
| | 2014 | 2013 | 2014 | 2013 |
| Personnel costs | $ 2,278 | $ 2,291 | $ 7,226 | $ 6,946 |
| Occupancy | 1,937 | 1,787 | 5,491 | 5,121 |
| Patent expenses | 882 | 695 | 1,962 | 3,769 |
| Depreciation and amortization | 548 | 589 | 1,697 | 1,886 |
| Insurance | 305 | 273 | 898 | 840 |
| Other | 779 | 813 | 2,502 | 2,481 |
| Non-cash compensation expense related to equity awards | 1,485 | 659 | 4,378 | 1,771 |
| Total antisense drug development | $ 8,214 | $ 7,107 | $ 24,154 | $ 22,814 |

R&D support costs for the three and nine months ended September 30, 2014 were $6.7 million and $19.8 million, respectively, compared to $6.4 million and $21.0 million for the same periods in 2013. Patent expenses were higher in 2013 primarily due to litigation costs for our patent infringement lawsuit against Santaris Pharma A/S. All amounts exclude non-cash compensation expense related to equity awards.

***General and Administrative Expenses***

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

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

| | Three Months Ended September 30, | | Nine Months Ended September 30, | |
|---|---|---|---|---|
| | 2014 | 2013 | 2014 | 2013 |
| General and administrative expenses | $ 2,958 | $ 2,991 | $ 9,298 | $ 9,094 |
| Non-cash compensation expense related to equity awards | 1,512 | 439 | 4,015 | 1,147 |
| Total general and administrative expenses | $ 4,470 | $ 3,430 | $ 13,313 | $ 10,241 |

General and administrative expenses were $3.0 million and $9.3 million, respectively, for the three and nine months ended September 30, 2014, and were essentially flat compared to $3.0 million and $9.1 million for the same periods in 2013. All amounts exclude non-cash compensation expense related to equity awards.

***Investment Income***

Investment income for the three and nine months ended September 30, 2014 was $675,000 and $2.0 million, respectively, compared to $434,000 and $1.4 million for the same periods in 2013. The increase in investment income was primarily due to a higher average cash balance and market conditions during the first nine months of 2014.

***Interest Expense***

Interest expense for the three and nine months ended September 30, 2014 was $5.0 million and $14.9 million, respectively, and was essentially flat compared to $4.9 million and $14.5 million for the same periods in 2013.

***Gain on Investments, net***

We recorded a gain on investments of $538,000 and $675,000 for the three and nine months ended September 30, 2014, respectively, compared to a gain on investments of $175,000 and $2.1 million for the same periods in 2013. The gain on investments for the first nine months of 2014 was primarily due to proceeds we received in the third quarter of 2014 when we sold a portion of the stock we held in several of our satellite companies. The net gain on investments in the first nine months of 2013 was primarily due to $1.1 million we received in the first quarter of 2013 when we sold the stock we held in Sarepta Therapeutics, Inc. and the $844,000 payment we received from Pfizer, Inc. in the second quarter of 2013 related to its acquisition of Excaliard Pharmaceuticals, Inc.

In November 2014, Regulus completed a public offering. As part of the offering, we sold 1,279,411 shares of Regulus' common stock for total proceeds of $20.4 million, resulting in a $17.8 million gain, which we will recognize in the fourth quarter of 2014.

***Income Tax Benefit***

We recorded tax expense of $1.4 million and $2,000 for the three months and nine months ended September 30, 2014, compared to a tax benefit of $5.2 million and $6.4 million for the same periods in 2013. Accounting rules require us to allocate our provision for income taxes between continuing

operations and other categories of earnings, such as other comprehensive income. In periods in which we have a year-to-date pre-tax loss from continuing operations and pre-tax income in other categories of earnings, such as other comprehensive income, we must allocate the tax provision to the other categories of earnings. We then record a related tax benefit in continuing operations. The tax benefit we recorded in the first nine months of 2013 is primarily related to the unrealized gains associated with our investments in Regulus.

***Net Loss and Net Loss per Share***

Net loss for the three and nine months ended September 30, 2014 was $26.7 million and $70.0 million, respectively, compared to $24.6 million and $36.4 million for the same periods in 2013. Basic and diluted net loss per share for the three and nine months ended September 30, 2014 was $0.23 and $0.60 per share, respectively, compared to $0.21 and $0.33 per share for the same periods in 2013. Our net loss increased in the first nine months of 2014 primarily due to the planned increase in operating expenses associated with our maturing pipeline of drugs, offset in part by higher revenue.

**Liquidity and Capital Resources**

We have financed our operations with revenue primarily from research and development collaborative agreements. Additionally, we have earned revenue from the sale or licensing of our intellectual property. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From our inception through September 30, 2014, we have earned approximately $1.4 billion in revenue from contract research and development and the sale and licensing of our intellectual property. From the time we were founded through September 30, 2014, we have raised net proceeds of approximately $1.1 billion from the sale of our equity securities and we have borrowed approximately $786.9 million under long-term debt arrangements to finance a portion of our operations.

At September 30, 2014, we had cash, cash equivalents and short-term investments of $592.0 million and stockholders' equity of $344.8 million. In comparison, we had cash, cash equivalents and short-term investments of $656.8 million and stockholders' equity of $378.4 million at December 31, 2013. Our cash balance at September 30, 2014 did not include approximately $23.5 million in payments that we recognized into revenue in the third quarter and received in the fourth quarter and $20.4 million of proceeds we received in November 2014 from participating in Regulus' recently completed equity offering. At September 30, 2014, we had consolidated working capital of $573.8 million, compared to $637.7 million at December 31, 2013. The decrease in our cash and working capital primarily relates to cash used to fund our operations.

As of September 30, 2014, our debt and other obligations totaled $280.6 million compared to $283.5 million at December 31, 2013. The decrease was primarily due to rent and principal payments we made in the first nine months of 2014 on our lease obligations and notes payable.

The following table summarizes our contractual obligations as of September 30, 2014. 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** |
| 2¾ percent Convertible Senior Notes (principal and interest payable) | $ 231.7 | $ 5.5 | $ 11.1 | $ 11.1 | $ 204.0 |
| Facility Rent Payments | $ 133.3 | $ 6.2 | $ 13.0 | $ 13.8 | $ 100.3 |
| Equipment Financing Arrangements (principal and interest payable) | $ 4.3 | $ 3.6 | $ 0.7 | $ - | $ - |
| Other Obligations (principal and interest payable) | $ 1.3 | $ 0.1 | $ 0.1 | $ 0.1 | $ 1.0 |
| Capital Lease | $ 0.2 | $ 0.2 | $ - | $ - | $ - |
| Operating Leases | $ 25.6 | $ 1.6 | $ 3.0 | $ 3.0 | $ 18.0 |
| Total | $ 396.4 | $ 17.2 | $ 27.9 | $ 28.0 | $ 323.3 |

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

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

In October 2008, we entered into an equipment financing loan agreement and in September 2009 and June 2012, we amended the loan agreement to increase the aggregate maximum amount of principal we could draw under the agreement. Each draw down under the loan agreement has a term of three years, with principal and interest payable monthly. Interest on amounts we borrow under the loan agreement is based upon the three year interest rate swap at the time we make each draw down plus 3.5 or four percent, depending on the date of the draw. We are using the equipment purchased under the loan agreement as collateral. As of September 30, 2014, 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 September 30, 2014 and December 31, 2013 was $4.2 million and $7.5 million, respectively. We will continue to use equipment lease financing as long as the terms remain commercially attractive.

In March 2010, we entered into a lease agreement with an affiliate of BioMed Realty, L.P. Under the lease, BioMed constructed a new facility in Carlsbad, California. The lease has an initial term of 20 years with an option to extend the lease for up to four five-year periods. Our rent under this lease is based on a percentage of the total construction costs spent by BioMed to acquire the land and build the new facility. To gain early access to the facility, we agreed to modify our lease with BioMed to accept additional responsibility. As a result, accounting rules required us to record the cost of the facility as a fixed asset with a corresponding liability. We are depreciating the building over its economic life and we apply our rent payments, which began on January 1, 2012, against the liability over the term of the lease.

In addition to contractual obligations, we had outstanding purchase orders as of September 30, 2014 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, 2013.*

## Risks Associated with our Drug Discovery and Development Business

**If the market does not accept KYNAMRO and our other drugs, including ISIS-APOCIII$_{Rx}$, 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 ISIS-APOCIII$_{Rx}$, 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 ISIS-APOCIII$_{Rx}$, 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 ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, unaffordable.

**If we fail to compete effectively, our drugs, including KYNAMRO, ISIS-APOCIII$_{Rx}$, 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, ISIS-APOCIII$_{Rx}$, 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, ISIS-APOCIII$_{Rx}$, 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 to provide this capability.

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

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 pradigastat and CAT-2003 could compete with ISIS-APOCIII$_{Rx}$, and the 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 ISIS-APOCIII$_{Rx}$, 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. Even if approved, we or our partners may not obtain the labeling claims necessary or desirable for successfully commercializing our drug products, including KYNAMRO, which is approved, ISIS-APOCIII$_{Rx}$, 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, ISIS-APOCIII$_{Rx}$, 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 ISIS-APOCIII$_{Rx}$, 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 ISIS-APOCIII$_{Rx}$, 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, ISIS-APOCIII$_{Rx}$, 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, ISIS-APOCIII$_{Rx}$, 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, ISIS-APOCIII$_{Rx}$, 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 ISIS-APOCIII$_{Rx}$, 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 ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$. If any of our drugs in clinical studies, including KYNAMRO, ISIS-APOCIII$_{Rx}$, 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 ISIS-APOCIII$_{Rx}$, 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 ISIS-APOCIII$_{Rx}$, 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 ISIS-APOCIII$_{Rx}$, 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, ISIS-APOCIII$_{Rx}$, 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, ISIS-APOCIII$_{Rx}$, 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 ISIS-APOCIII$_{Rx}$, 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 September 30, 2014, we had an accumulated deficit of approximately $1.0 billion and stockholders' equity of approximately $344.8 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from research grants and the sale or licensing of our patents, as well as interest income. We 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, Biogen Idec, 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, Biogen Idec, 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, ISIS-APOCIII$_{Rx}$, 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 ISIS-APOCIII$_{Rx}$, 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 September 2011 we filed a patent infringement lawsuit against Santaris Pharma A/S and Santaris Pharma A/S Corp. in the United States District Court of the Southern District of California, and 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. These 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 unresolved.

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

Many of our drugs are undergoing clinical studies or are in the early stages of research and development. All of our drug programs will require significant additional research, development, preclinical and/or clinical testing, regulatory approval and/or commitment of significant additional resources prior to their successful commercialization. As of September 30, 2014, we had cash, cash equivalents and short-term investments equal to $592.0 million. If we do not meet our goals to successfully commercialize KYNAMRO and our other drugs, including ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{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 ISIS-APOCIII$_{Rx}$, 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 September 30, 2014, the market price of our common stock ranged from $22.25 to $62.66 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.

**We depend on Regulus for development of our microRNA technology.**

Regulus is a company that we and Alnylam established to focus on discovering, developing, and commercializing microRNA therapeutics. We exclusively licensed to Regulus our intellectual property rights covering microRNA technology. Regulus operates as an independent company and Regulus and its employees are responsible for researching and developing our microRNA technology. If Regulus is not successful, the value of our microRNA technology would be harmed and we would lose part or all of our investment in Regulus.

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

We manufacture our research and clinical supplies in a manufacturing facility located in Carlsbad, California. The facilities and the equipment we use to research, develop and manufacture our drugs would be costly to replace and could require substantial lead time to repair or replace. Our facilities may be harmed by natural or man-made disasters, including, without limitation, earthquakes, floods, fires and acts of terrorism; and if our facilities are affected by a disaster, our development and commercialization efforts would be delayed. Although we possess insurance for damage to our property and the disruption of our business from casualties, this insurance may not be sufficient to cover all of our potential losses and may not continue to be available to us on acceptable terms, or at all. In addition, our development and commercialization activities could be harmed or delayed by a 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 12.1 million shares of our common stock upon conversion of our convertible senior notes. The addition of any of these shares into the public market may have an adverse effect on the price of our securities.

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

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

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

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

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

## ITEM 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

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

## ITEM 4. CONTROLS AND PROCEDURES

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

As of our most recently completed fiscal year and as of the end of the period covered by this Quarterly Report on Form 10-Q, we carried out an evaluation of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. Based on our evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of September 30, 2014. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to September 30, 2014.

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

***Santaris Litigation***

In September 2011, we filed a patent infringement lawsuit against Santaris Pharma A/S and Santaris Pharma A/S Corp. in the United States District Court of the Southern District of California. Our infringement lawsuit alleges that Santaris' activities providing antisense drugs and antisense drug discovery services to several pharmaceutical companies infringes U.S. Patent No. 6,326,199, entitled "Gapped 2' Modified Oligonucleotides" and U.S. Patent No. 6,066,500, entitled "Antisense Modulation of Beta Catenin Expression." In the lawsuit we are seeking monetary damages and an injunction enjoining Santaris from conducting or participating in the infringing activities. In December 2011, Santaris filed an answer to our complaint, denying our allegations, and seeking a declaration from the court that Santaris has not, and does not, infringe the patents we asserted against Santaris in the suit. In January 2012, Santaris filed a motion for summary judgment asking the court to decide as a matter of law that Santaris' activities do not infringe the patents we assert in the suit. In September 2012, the court denied Santaris' motion for summary judgment and opened limited discovery related to whether Santaris' alleged infringing activities are permitted by the safe harbor under 35 U.S.C. Section 271(e)(1). In April 2013, we amended our complaint related to the lawsuit to include additional claims alleging that Santaris' activities providing antisense drugs and antisense drug discovery services to a pharmaceutical company infringes U.S.

Patent No. 6,440,739 entitled “Antisense Modulation of Glioma-Associated Oncogene-2 Expression”; and that Santaris induced its actual and prospective pharmaceutical partners to infringe U.S. Patent No. 6,326,199. In December 2013, Santaris filed a new motion for summary judgment asking the court to decide as a matter of law that Santaris’ alleged infringing activities are permitted by the safe harbor under 35 U.S.C. Section 271(e)(1). On February 27, 2014, the court denied this motion.

In March 2014, Santaris filed a motion asking the court to decide that Santaris’ alleged infringing sales of Isis’ patented methods are not actionable as a matter of law. In June 2014, the court granted Santaris’ motion and dismissed our allegations to the extent the allegations are based on Santaris’ sale or offer for sale of such method claims; and that we did not plead sufficient facts to establish that Santaris entering into its agreement with Enzon constituted the sale or offer for sale of the compounds claimed in U.S. Patent No. 6,066,500 and U.S. Patent No. 6,440,739. The rest of the case is proceeding, and on October 17, 2014, we filed an amended complaint to plead additional facts and assert Santaris infringed U.S. Patent No. 6,066,500 and U.S. Patent No. 6,440,739 through Santaris' agreement with Enzon.

***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. Isis and Merck Sharp & Dohme Corp. filed their 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 Isis' agreement with Merck, Merck is responsible for the costs of this suit.

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

Not applicable.

**ITEM 3. DEFAULT UPON SENIOR SECURITIES**

Not applicable.

**ITEM 4. MINE SAFETY DISCLOSURES**

Not applicable.

**ITEM 5. OTHER INFORMATION**

Not Applicable.

**ITEM 6. EXHIBITS**

a. Exhibits

| Exhibit Number | Description of Document |
|---|---|
| 10.1 | Exclusive License Agreement between the Registrant and the University of Massachusetts dated January 14, 2010. Portions of this exhibit have been omitted and separately filed with the SEC. |
| 10.2 | Amended and Restated Collaboration and License Agreement between the Registrant and Cold Spring Harbor Laboratory dated October 26, 2011. Portions of this exhibit have been omitted and separately filed with the SEC. |
| 10.3 | Amendment to Amended and Restated Collaboration and License Agreement between the Registrant and Cold Spring Harbor Laboratory dated March 14, 2014. Portions of this exhibit have been omitted and separately filed with the SEC. |
| 31.1 | Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002. |
| 31.2 | Certification by Chief Financial Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002. |
| 32.1 | Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002. |
| 101 | The following financial statements from the Isis Pharmaceuticals, Inc. Quarterly Report on Form 10-Q for the quarter ended September 30, 2014, formatted in Extensive Business Reporting Language (XBRL): (i) condensed consolidated balance sheets, (ii) condensed consolidated statements of operations, (iii) condensed consolidated statements of comprehensive loss, (iv) condensed consolidated statements of cash flows and (v) notes to condensed consolidated financial statements (detail tagged). |

**Isis Pharmaceuticals, Inc.**

(Registrant)

**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<br>Stanley T. Crooke, M.D., Ph.D. | Chairman of the Board, President, and Chief Executive Officer<br>(Principal executive officer) | November 7, 2014 |
| /s/ Elizabeth L. Hougen<br>Elizabeth L. Hougen | Senior Vice President, Finance and Chief Financial Officer<br>(Principal financial and accounting officer) | November 7, 2014 |

EXHIBIT 10.1

UMass Agreement No: UMMS 05-19-03

**EXCLUSIVE LICENSE AGREEMENT**

This Exclusive License Agreement (the "Agreement"), effective as of January 14, 2010 (the "Effective Date"), is between the **UNIVERSITY OF MASSACHUSETTS** ("University"), a public institution of higher education of the Commonwealth of Massachusetts as represented by its Worcester campus, and **ISIS PHARMACEUTICALS, INC.** ("Isis"), a Delaware corporation.

**RECITALS**

WHEREAS, University owns intellectual property rights which relate to certain technology as described in University's invention disclosure [***];

WHEREAS, Isis is a drug discovery and development company and has the capability of developing commercial applications of the intellectual property;

WHEREAS, Isis desires to obtain an exclusive license to University's intellectual property rights, and University is willing to grant an exclusive license to its intellectual property rights under the following conditions so that these intellectual property rights may be developed to their fullest and the benefits enjoyed by the general public; and

WHEREAS, the license that is granted in this Agreement promotes the development of publicly funded intellectual property to practical application for the public good.

THEREFORE, University and Isis agree as follows:

1. Definitions.

1.1. "Approval" means, with respect to any Licensed Product in the United States, approval from the FDA sufficient for the manufacture, distribution, use and sale of the Licensed Product in accordance with applicable laws.

1.2. "Commercially Reasonable Efforts" means, with regard to the development of a Licensed Product, either (a) achievement of any of the diligence events in accordance with Section 3.1(b)(i) of this Agreement, or (b) the expenditure of the annual Minimum Spend in accordance with Section 3.1(b)(ii) of this Agreement.

1.3. "Confidential Information" means any confidential or proprietary information furnished by one party (the "Disclosing Party") to the other party (the "Receiving Party") in connection with this Agreement that is specifically designated as confidential, as further described in Article 7.

1.4. "FDA" means the United States Food and Drug Administration and any successor agency thereto.

1.5. "Field" means the treatment of spinal muscular atrophy and/or amyotrophic lateral sclerosis in humans.

1.6. "First Commercial Sale" means the first sale of a Licensed Product by Isis or a Sublicensee to a Third Party.

1.7. "First Human Dose" means the first instance in which a dose of a Licensed Product is administered to a human being in a clinical trial.

1.8. "IND" means an Investigational New Drug Application filed with the FDA as described in 21 C.F.R. Part 312.

1.9 "Initiation of a Phase II Clinical Trial" means the enrollment of the first human subject in a Phase II Clinical Trial.

1.10. "Initiation of a Phase III Clinical Trial" means the enrollment of the first human subject in a Phase III Clinical Trial.

1.11. "Licensed Product" means any product that cannot be developed, manufactured, used, or sold without infringing one or more Valid Claims. [***].

1.12 "NDA" means a New Drug Application as described in 21 C.F.R. Part 314, filed with the FDA after completion of clinical trials to obtain Approval for a Licensed Product in the United States.

1.13. "NDA Filing" means submission of an NDA to the FDA for a Licensed Product.

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

In any transfers of Licensed Products between Isis and its Sublicensees, Net Sales are calculated based on the final sale of the Licensed Product to an independent Third Party. If Isis or a Sublicensee receives non-monetary consideration for any Licensed Products, Net Sales are calculated based on the fair market value of that consideration. If Isis or its Sublicensees uses or disposes of a Licensed Product in the provision of a commercial service, the Licensed Product is sold and the Net Sales are calculated based on the sales price of the Licensed Product to an independent Third Party during the same Royalty Period or, in the absence of sales, on the fair market value of the Licensed Product as determined by the parties in good faith. Net Sales shall not include any transfers of supplies of the applicable Licensed Product for (i) use in clinical trials, pre-clinical studies or other research or development activities, or (ii) for a bona fide charitable purpose; or (iii) for or a commercially reasonable sampling program.

1.15. "Orphan Drug Status" means, with respect to a Licensed Product, that (i) the Secretary of the FDA has (1) approved an application filed pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act ("FD&C Act"), (2) issued a certification under section 507 of the FD&C Act, or (3) issued a license under section 351 of the Public Health Service Act for such Licensed Product designated under section 526 of the FD&C Act for a rare disease or condition, and (ii) the Licensed Product has obtained market exclusivity under section 505A of the Food and Drug Administration Modernization Act of 1997.

1.16 "Patent Rights" means the United States patent applications listed in Exhibit A, and any divisional, continuation, or continuation-in-part, and requests for continued examination of that patent application to the extent the claims are directed to subject matter specifically described therein as well as any patents issued on these patent applications and any reissues or reexaminations or extensions of the patents.

1.17. "Phase II Clinical Trial" means a human clinical trial of a Licensed Product that satisfies the requirements of 21 CFR 312.21(b).

1.18. "Phase III Clinical Trial" means a human clinical trial of a Licensed Product that satisfies the requirements of 21 CFR 312.21(c)..

1.19. "Registration Trial" means any human clinical trial under 21 CFR 312.21 designed to provide, or that does provide, data sufficient to file an NDA.

1.20. "Royalty Period" means the partial calendar quarter commencing on the date on which the first Licensed Product is sold or commercially used and every complete or partial calendar quarter thereafter during which either (a) this Agreement remains in effect or (b) Isis has the right to complete and sell work-in-progress and inventory of Licensed Products pursuant to Section 8.5.

1.21. "Royalty Term" has the meaning set forth in Section 4.5.

1.22. "Sublicense Agreement" means any agreement in which Isis grants rights to the Patent Rights pursuant to Section 2.2.

1.23. "Sublicense Income" means any consideration Isis receives from a Sublicensee in consideration for the grant of any Sublicense, including, but not limited to, license fees, up-front payments, and license maintenance fees, but excluding: (i) royalties or profit-sharing payments based on commercial sales of the Licensed Product, (ii) payments made in consideration of equity or debt securities of Isis at fair market value, (iii) payments specifically committed to reimburse Isis for the cost of research and/or development of Licensed Products, (iv) payments dedicated to reimburse IP/Patent expenses, and (v) payments made to Isis that Isis forwards to a Third Party to which Isis owes a financial obligation (such as a milestone payment to a Third Party licensor applicable to a Licensed Product).

1.24. "Sublicensee" means any permitted sublicensee of the rights granted Isis under this Agreement, as further described in Section 2.2.

1.25. "Third Party" means any person or legal entity other than University or Isis.

1.26. "Valid Claim" means (a) a claim of an issued and unexpired patent covering the Patent Rights which has not been permanently revoked or held unenforceable or invalid by an unappealable or unappealed decision of a court or government agency of competent jurisdiction or (b) a claim of a pending patent application within the Patent Rights that has not been abandoned or finally disallowed without the possibility of appeal or refiling.

2. Grant of Rights.

2.1. License Grant. University grants to Isis an exclusive, royalty-bearing license in the United States under the Patent Rights to develop, make, have made, use, sell, offer for sale, have sold, import, and export Licensed Products in the Field.

2.2. Sublicenses. Isis may not grant a sublicense of its rights under Section 2.1 without first obtaining the University's consent to the proposed Sublicensee, which consent may not be unreasonably withheld or delayed; *provided, however*, University hereby provides its consent in advance for Isis to grant a sublicense of its rights under Section 2.1 to [***] (or its successor). University will use good-faith efforts to provide a response to any such consent request as soon as reasonably practicable; *provided, however*, if University fails to respond to Isis within [***] days of University's receipt of such consent request, such consent will be deemed to have been affirmatively provided by the University for purposes of this Section 2.2. All Sublicense Agreements executed by Isis pursuant to this Section 2.2 shall expressly state that such Sublicense Agreement is subject to the terms of this Agreement. Isis shall promptly furnish University with a fully executed copy of any Sublicense Agreement, and any such Sublicense Agreement will be treated as the Confidential Information of Isis in accordance with Section 7.1. Sublicenses granted pursuant to this Section 2.2 shall survive the termination of this Agreement, *provided, however* that Sublicensees agree to modify the Sublicense Agreements to conform with this Agreement and to reflect University's status as a tax-exempt educational and research institution. [***].

2.3. Retained Rights.

(a) University. University retains the right to use the Patent Rights for non-commercial purposes, including academic research, teaching, and patient care, without payment of compensation to Isis. University may license such retained rights under this Subsection 2.3(a) to research collaborators of University faculty members, post-doctoral fellows, and students for such purposes.

(b) Federal Government. If the federal government has funded any invention claimed in the Patent Rights, this Agreement and the grant of any rights in Patent Rights are subject to the federal law set forth in 35 U.S.C. §§ 201-211 and the regulations promulgated thereunder, as amended, or any successor statutes or regulations. Isis acknowledges that these statutes and regulations reserve to the federal government a royalty-free, non-exclusive, non-transferrable license to practice any government-funded invention claimed in the Patent Rights. If any term of this Agreement fails to conform to those laws and regulations, the relevant term is invalid, and the parties shall modify the term pursuant to Section 10.11.

(c) Other Organizations. If a non-profit organization or state or local agency has funded any invention claimed in the Patent Rights, this Agreement and the grant of any rights in the Patent Rights are subject to the terms of the applicable research grants. To the extent any term of this Agreement fails to conform with those terms, the relevant term shall be modified by the parties pursuant to Section 10.11. In the event University discovers a research grant that requires modification of this Agreement pursuant to Section 10.11, University shall promptly notify Isis thereof.

3. Isis Obligations Relating to Commercialization.

3.1. Diligence Requirements. Isis shall use Commercially Reasonable Efforts or cause its Sublicensees to use Commercially Reasonable Efforts to develop Licensed Products and to introduce Licensed Products into the commercial market. Thereafter, Isis or its Sublicensees shall make Licensed Products reasonably commercially available to the public. Specifically, Isis shall fulfill the following obligations:

(a) General Obligations.

(i) Within [***] ([***]) days after execution of this Agreement, Isis shall furnish University with a [***]. University acknowledges and agrees that this [***] is a [***] of Isis' current intention regarding the [***] and that [***].

(ii) Within [***] ([***]) days after the start of each calendar year, beginning on January 1, 2011, Isis shall furnish University with a written report on progress during the prior year to develop and commercialize Licensed Products, including without limitation research and development, efforts to obtain regulatory approval, marketing, and sales figures. Isis shall also include in the report a discussion of its intended development and commercialization efforts and sales projections, if any, for the current year.

(b) Development of Licensed Products.

(i) Diligence Events.

a. Within [***] ([***]) years after the Effective Date, Isis or its Sublicensee shall [***] covering at least one (1) Licensed Product.

b. Within [***] ([***]) years after the Effective Date, Isis or its Sublicensee shall [***] covering at least one (1) Licensed Product.

c. Within [***] ([***]) years after the Effective Date, Isis or its Sublicensee shall [***] covering at least one (1) Licensed Product.

d. Within [***] ([***]) years after the Effective Date, Isis or its Sublicensee shall [***] covering at least one (1) Licensed Product.

e. Within [***] ([***]) months after [***] for any Licensed Product, Isis or its Sublicensee shall [***].

(ii) Minimum Spend. During the Term of this Agreement and until the occurrence of [***] for a Licensed Product, in developing a Licensed Product, Isis or its Sublicensee shall spend annually an aggregate amount of at least [***] dollars ($[***]) consisting of [***] ("Minimum Spend"). Both University and Isis acknowledge that, because the nature and amount of tasks associated with development of the Licensed Product shall vary from year-to-year, the amount of [***] and [***] expenditure shall also vary year-to-year, with some years exceeding the Minimum Spend and some years not. Achievement of either a diligence event under Subsection 3.1(b)(i) or the Minimum Spend under this Subsection 3.1(b)(ii) shall be deemed dispositive of using Commercially Reasonable Efforts.

3.2. Dispute Resolution. If University determines that Isis has not fulfilled its obligations under Subsection 3.1(b), University shall furnish Isis with written notice of the determination. Within [***] ([***]) days after receipt of the notice, Isis shall either (a) fulfill the relevant obligation or (b) negotiate with University a mutually acceptable schedule of revised diligence events or Minimum Spend. In the event University and Isis are unable to reach a mutually acceptable resolution, the dispute shall be referred to senior executives of each party, who shall meet at a mutually acceptable time and location within [***] ([***]) days after expiration of the specified [***] ([***]) day period and attempt to negotiate a settlement which may include a different Minimum Spend or a new diligence event timeline. In the event the designated senior executives are not able to resolve such dispute during such [***] ([***]) day period, then the affected party, upon written notice to the other party, may initiate arbitration pursuant to Section 9.2(b).

3.3. Indemnification.

(a) Indemnity. Isis shall indemnify, defend, and hold harmless University and its trustees, officers, faculty, students, employees, and agents and their respective successors, heirs and assigns (the "Indemnitees"), against any liability, damage, loss, or expense (including reasonable attorneys' fees and expenses of litigation) incurred by or imposed upon any of the Indemnitees in connection with any claims, suits, actions, demands or judgments arising out of any theory of liability (including without limitation actions in the form of tort, warranty, or strict liability and regardless of whether the action has any factual basis) concerning any product, process, or service that is made, used, or sold pursuant to any right or license granted under this Agreement. However, indemnification does not apply to any liability, damage, loss, or expense to the extent directly attributable to (i) the gross negligence or intentional misconduct of the Indemnitees or (ii) the settlement of a claim, suit, action, or demand by Indemnitees without the prior written approval of Isis.

(b) Procedures. The Indemnitees agree to provide Isis with prompt written notice of any claim, suit, action, demand, or judgment for which indemnification is sought under this Agreement. Isis agrees, at its own expense, to provide attorneys reasonably acceptable to University to defend against any claim. The Indemnitees shall cooperate fully with Isis in the defense and will permit Isis to conduct and control the defense and the disposition of the claim, suit, or action (including all decisions relative to litigation, appeal, and settlement). However, any Indemnitee may retain its own counsel, at the expense of Isis, if representation of the Indemnitee by the counsel retained by Isis would be inappropriate because of actual or potential conflicts in the interests of the Indemnitee and any other party represented by that counsel. Isis agrees to keep University informed of the progress in the defense and disposition of the claim and to consult with University regarding any proposed settlement.

(c) Insurance. Isis shall maintain insurance or self-insurance that is reasonably adequate to fulfill any potential obligation to the Indemnitees, but not less than [***] dollars ($[***]) for injuries to any one person arising out of a single occurrence and [***] dollars ($[***]) for injuries to all persons arising out of a single occurrence. Isis shall provide University with written evidence of insurance or self-insurance. Isis shall continue to maintain the insurance or self-insurance after the expiration or termination of this Agreement while Isis or its Sublicensee continues to make, use, or sell a Licensed Product and thereafter for [***] ([***]) years.

3.4. Use of University's Name. In accordance with Section 7.2., Isis and its Sublicensees may not use the name "University of Massachusetts" or any variation of that name in connection with the marketing or sale of any Licensed Products.

3.5. Marking of Licensed Products. To the extent commercially feasible and consistent with prevailing business practices, Isis shall mark and shall cause its Sublicensees to mark all Licensed Products that are manufactured or sold under this Agreement with the number of each issued patent under the Patent Rights that applies to a Licensed Product.

3.6. Compliance with Law. Isis shall comply with, and shall ensure that its Sublicensees comply with, all local, state, federal, and international laws and regulations applicable to the development, manufacture, use, and sale of Licensed Products. Isis expressly agrees to comply with the following:

(a) Isis or its Sublicensees shall obtain all necessary approvals from the United States Food & Drug Administration and any similar foreign governmental authorities in which Isis or its Sublicensee intends to make, use, or sell Licensed Products.

(b) Isis and its Sublicensees shall comply with all United States laws and regulations controlling the export of commodities and technical data, including without limitation all Export Administration Regulations of the United States Department of Commerce. Among other things, these laws and regulations prohibit or require a license for the export of certain types of commodities and technical data to specified countries and foreign nationals. Isis hereby gives written assurance that it shall comply with and shall cause its Sublicensees to comply with all United States export control laws and regulations, that it bears sole responsibility for any violation of those laws and regulations by itself or its Sublicensees, and that it shall indemnify, defend, and hold University harmless (in accordance with Section 3.3.) for the consequences of any violation.

(c) If any invention claimed in the Patent Rights has been funded by the United States government, and only to the extent required by applicable laws and regulations, Isis agrees that any Licensed Products used or sold in the United States shall be manufactured substantially in the United States or its territories. Current law provides that if domestic manufacture is not commercially feasible under the circumstances, University may seek a waiver of this requirement from the relevant federal agency on behalf of Isis and, if requested in writing by Isis, University shall, at Isis' expense, seek such a waiver for the benefit of Isis.

4. Consideration for Grant of Rights.

4.1. License Fee. In partial consideration of the rights granted Isis under this Agreement, Isis shall pay to University within [***] ([***]) days of the Effective Date a license fee of [***] dollars ($[***]). This license fee payment is nonrefundable and is not creditable against any other payments due to University under this Agreement.

4.2. This Section Intentionally Left Blank.

4.3. License Maintenance Fee. Within [***] ([***]) days of each anniversary of the Effective Date, during the term of this Agreement, Isis shall pay to University [***] Dollars ($[***]). This annual license maintenance fee is nonrefundable and is not creditable against any other payments due to University under this Agreement.

4.4. Milestone Payments. Isis shall pay University the following milestone payments within [***] ([***]) days after the first occurrence of each event:

| Event | Payment |
|---|---|
| [***] | $[***] |
| [***] | $[***] |
| [***] | $[***] |

These milestone payments are nonrefundable and are not creditable against any other payments due to University under this Agreement. Each milestone payment shall be payable only once, irrespective of the number of Licensed Products to achieve the milestone event. [***].

In the event Isis enters into a Sublicense Agreement that grants rights to develop and commercialize a Licensed Product in the United States pursuant to Section 2.2, [***].

4.5. Royalties. The Parties acknowledge that University's standard licensing practice aims for the development of a Licensed Product in accordance with specific time frames (such as those enumerated in Section 3.1(b)) in part by providing for immediate termination of a license agreement under certain circumstances. In lieu of such a provision in this Agreement, the Parties agree in part to the payment of royalties as specified below during the Royalty Term, which for the purposes of this Agreement, shall mean the period commencing on the date of First Commercial Sale of a Licensed Product after Approval and ending on the date that is the later of (i) [***]; or (ii) [***] (the "Royalty Term").

a. Base Royalty Rate. Subject to Subsection 4.5 (b) below, during the Royalty Term, Isis shall pay to University a royalty of [***] percent ([***]%) of Net Sales of Licensed Products occurring during the Royalty Term.

b. Royalty Step Down in the Absence of Orphan Status and Valid Claims. In the event a Licensed Product (i) does not have Orphan Drug Status; and (ii) is not covered by a Valid Claim, then Isis shall pay University a royalty of [***] percent ([***]%) of Net Sales of said Licensed Product during the Royalty Term. However, for the removal of doubt, in the event a Licensed Product (i) has Orphan Drug Status, and (ii) is not covered by a Valid Claim, then Isis shall pay University a royalty of [***] percent ([***]%) of Net Sales of Licensed Products during the Royalty Term.

4.6. Minimum Royalty.

a. Prior to [***]. Within [***] ([***]) days after the beginning of each calendar year during the term of this Agreement, beginning [***] and ending on the earlier of (i) [***] or (ii) the date of [***], an annual minimum royalty ("Minimum Royalty") of [***] Dollars ($[***]) shall accrue but not be payable to University until [***]. Isis may not [***] under any circumstance unless and until it has [***].

b. After [***]. Within [***] ([***]) days after the beginning of each calendar year during the Term of this Agreement following [***], Isis shall pay University a Minimum Royalty according to the following schedule:

| | |
|---|---|
| Years [***]: | $[***] |
| Years [***]: | $[***] |
| Years [***]: | $[***] |
| Years [***]: | $[***] |

Isis may credit the Minimum Royalty paid under this Section 4.6(b) against actual royalties due and payable for the same calendar year in which such Minimum Royalty is paid. Further, with respect to Minimum Royalties accrued under Section 4.6(a), Isis may credit only those Minimum Royalties that have accrued for the same calendar year as actual royalties are due and payable. Waiver of any Minimum Royalty payment by University is not a waiver of any subsequent Minimum Royalty payment. If Isis fails to make any Minimum Royalty payment within the [***] period, that failure is a material breach of its obligations under this Agreement, and University may terminate this Agreement if such breach is not cured in accordance with Section 8.3.

4.7. Sublicense Income. If Isis enters into a Sublicense Agreement, Isis shall pay University the percentages of all Sublicense Income received by Isis as consideration for such Sublicense Agreement, as set forth below in Table 4.7. The calculation of such Sublicense Income payment is based upon the status of the Licensed Product at the time Isis sublicenses it to a Third Party, as described in Table 4.7 below.

**Table 4.7**

| **Status of Licensed Product Upon Sublicense to Third Party** | **Percentage of Sublicense Income to be Paid to University** |
|---|---|
| [***] | [***]% |
| [***] | [***]% |
| [***] | [***]% |

All payments under this Section 4.7 are due within [***] ([***]) days after Isis receives the relevant payment from the Sublicensee. Any Sublicense Income paid by Isis will be creditable against the milestone payments payable by Isis to University under Section 4.4.

5. Royalty Reports; Payments; Records.

5.1. First Sale. Isis shall report to University the date of First Commercial Sale of each Licensed Product within [***] ([***]) days after occurrence in the United States.

5.2. Reports and Payments.

(a) Within [***] ([***]) days after the conclusion of each Royalty Period, Isis shall deliver to University a report containing the following information:

(i) the number of Licensed Products sold to independent Third Parties in the United States and the number of Licensed Products used by Isis and its Sublicensees in the provision of commercial services in the United States;

(ii) the gross sales price for each Licensed Product by Isis and its Sublicensees during the applicable Royalty Period in the United States;

(iii) calculation of Net Sales for the applicable Royalty Period in the United States, including a listing of applicable deductions;

(iv) total royalty payable on Net Sales in United States dollars, together with the exchange rates, if any, used for conversion; and

(v) Sublicense Income due to University for the applicable Royalty Period from each Sublicensee.

(b) Concurrent with this report, Isis shall remit to University any payment due for the applicable Royalty Period. If no royalties are due to University for any Royalty Period, the report shall so state.

5.3. Payments in United States Dollars. Isis shall make all payments in United States dollars. Isis shall convert foreign currency to United States dollars at the conversion rate existing in the United States (as reported in the *Wall Street Journal*) on the last working day of the calendar quarter preceding the applicable Royalty Period. Isis may not deduct exchange, collection, or other charges.

5.4. Payments in Other Currencies. If by law, regulation, or fiscal policy of a particular country, conversion into United States dollars or transfer of funds of a convertible currency to the United States is restricted or forbidden, Isis shall give University prompt written notice of the restriction within the [***] payment deadline described in Section 5.2. Isis shall pay any amounts due University through whatever lawful methods University reasonably designates. However, if University fails to designate a payment method within [***] ([***]) days after University is notified of the restriction, Isis may deposit payment in local currency to the credit of University in a recognized banking institution selected by Isis and identified by written notice to University, and that deposit fulfills all obligations of Isis to University with respect to that payment.

5.5. Records. Isis shall maintain and shall cause its Sublicensees to maintain complete and accurate records of Licensed Products that are made, used, or sold under this Agreement and any amounts payable to University in relation to Licensed Products with sufficient information to permit University to confirm the accuracy of any reports delivered to University under Section 5.2. The relevant party shall retain records relating to a given Royalty Period for at least [***] ([***]) years after the conclusion of that Royalty Period, during which time University may, at its expense, cause its internal accountants or an independent, certified public accountant to inspect records during normal business hours for the sole purpose of verifying any reports and payments delivered under this Agreement. The accountant may not disclose to University any information other than information relating to accuracy of reports and payments delivered under this Agreement. The parties shall reconcile any underpayment or overpayment within [***] ([***]) days after the accountant delivers the results of the audit. If any audit performed under this Section 5.5 reveals an underpayment in excess of [***] percent ([***]%) in any Royalty Period, Isis shall bear the full cost of the audit. University may exercise its rights under this Section 5.5 only once every year and only with reasonable prior notice to Isis.

5.6. Late Payments. Any payments by Isis that are not paid on or before the date payments are due under this Agreement bear interest at [***]% per month, calculated on the number of days that payment is delinquent.

5.7. Method of Payment. All payments under this Agreement should be made to the “University of Massachusetts” and sent to the address identified below. Each payment should reference this Agreement and identify the obligation under this Agreement that the payment satisfies.

5.8. Withholding and Similar Taxes. The University is a tax-exempt entity under Section 115 of the Internal Revenue Code. So long as University is such a tax-exempt entity, royalty payments and other payments due to University under this Agreement may not be reduced by reason of any withholding or similar taxes applicable to payments to University. Therefore all amounts owed to University under this Agreement are net amounts and shall be grossed-up to account for any withholding taxes, value-added taxes or other taxes, levies or charges. University will promptly notify Isis in writing if University ceases to be such a tax-exempt entity.

6. Patents and Infringement.

6.1. Responsibility for Patent Rights.

(a) University has primary responsibility at the expense of Isis for the preparation, filing, prosecution, and maintenance of all Patent Rights, using patent counsel reasonably acceptable to Isis. University shall consult with Isis as to the preparation, filing, prosecution, and maintenance of all Patent Rights reasonably prior to any deadline or action with the United States Patent & Trademark Office or any foreign patent office and shall furnish Isis with copies of relevant documents reasonably in advance of consultation. University shall consider in good faith any comments of Isis on any patent filings for the Patent Rights. Additionally, at the request of Isis, Isis and University shall meet and confer in person or via teleconference/videoconference on a quarterly basis during the term of this Agreement to discuss patent prosecution matters.

(b) If University desires to abandon any patent or patent application within the Patent Rights, University shall provide Isis with reasonable prior notice of the intended abandonment, and Isis may, at its expense, prepare, file, prosecute, and maintain the relevant Patent Rights.

6.2. Cooperation. Each party shall provide reasonable cooperation in the preparation, filing, prosecution, and maintenance of all Patent Rights. Cooperation includes, without limitation, promptly informing the other party of matters that may affect the preparation, filing, prosecution, or maintenance of Patent Rights (such as, becoming aware of an additional inventor who is not listed as an inventor in a patent application).

6.3. Payment of Expenses.

(a) Within [***] ([***]) days after University invoices Isis, Isis shall reimburse University for all previously unreimbursed expenses incurred as of the Effective Date in connection with obtaining the Patent Rights.

(b) Within [***] ([***]) days after University invoices Isis, Isis shall reimburse University for all patent-related expenses that have not been paid under Subsection 6.3(a) and that are incurred by University pursuant to Section 6.1. Isis may elect, upon [***] ([***]) days' written notice to University, to cease payment of the expenses associated with obtaining or maintaining patent protection for one or more Patent Rights. If Isis elects to cease payment of any patent expenses, Isis loses all rights under this Agreement with respect to the particular Patent Rights.

6.4. Infringement.

(a) Notification of Infringement. Each party agrees to provide written notice to the other party promptly after becoming aware of any infringement of the Patent Rights.

(b) Isis Right to Prosecute. As long as Isis remains the exclusive licensee of the Patent Rights in the Field, Isis may, under its own control and at its own expense, prosecute any Third Party infringement of the Patent Rights in the Field or, together with licensees of the Patent Rights in other fields (if any), defend the Patent Rights in any declaratory judgment action brought by a Third Party which alleges invalidity, unenforceability, or infringement of the Patent Rights. Prior to commencing any action, Isis shall consult with University and shall consider the views of University regarding the advisability of the proposed action and its effect on the public interest. Isis may not enter into any settlement, consent judgment, or other voluntary final disposition of any infringement action under this Subsection 6.4(b) without the prior written consent of University, which consent may not be unreasonably withheld or delayed; Any recovery obtained in an action under this Subsection 6.4(b) shall be distributed as follows: (i) each party shall be reimbursed for any expenses incurred in the action (including the amount of any royalty payments withheld from University as described below); (ii) as to ordinary damages, Isis shall receive an amount equal to [***], less [***]; and (iii) as to special or punitive damages, the parties shall [***].

(c) University as Indispensable Party. University shall permit any action under Subsection 6.4(b) to be brought in its name if required by law, provided that Isis shall hold University harmless from, and if necessary indemnify University against, any costs, expenses, or liability that University may incur in connection with the action.

(d) University Right to Prosecute. If Isis fails to initiate an infringement action within a reasonable time after it first becomes aware of the basis for the action, or to answer a declaratory judgment action within a reasonable time after the action is filed, University may prosecute the infringement or answer the declaratory judgment action under its sole control and at its sole expense, and any recovery obtained shall be given to University. If University takes action under this Subsection 6.4(d), University shall keep Isis reasonably informed of material actions taken by University pursuant to the infringement or declaratory action.

(e) Cooperation. Both parties shall cooperate fully in any action under this Section 6.4. which is controlled by the other party, provided that the controlling party reimburses the cooperating party promptly for any reasonable costs and expenses incurred by the cooperating party in connection with providing assistance.

7. Confidential Information; Publications; Publicity.

7.1. Confidential Information.

(a) Designation. The Disclosing Party shall mark Confidential Information that is disclosed in writing with a legend indicating its confidential status (such as, “Confidential” or “Proprietary”). The Disclosing party shall document Confidential Information that is disclosed orally or visually in a written notice and deliver the notice to the Receiving Party within thirty (30) days of the date of disclosure. The notice shall summarize the Confidential Information that was disclosed and reference the time and place of disclosure.

(b) Obligations. For [***] ([***]) years after disclosure of any portion of Confidential Information, the Receiving Party shall (i) maintain Confidential Information in confidence, except that the Receiving Party may disclose or permit the disclosure of any Confidential Information to its trustees or directors, officers, employees, consultants, actual and potential Sublicensees, and advisors who are obligated to maintain the confidential nature of Confidential Information and who need to know Confidential Information for the purposes of this Agreement; (ii) use Confidential Information solely for the purposes of this Agreement; and (iii) allow its trustees or directors, officers, employees, consultants, actual and potential Sublicensees, and advisors to reproduce the Confidential Information only to the extent necessary for the purposes of this Agreement, with all reproductions being Confidential Information.

(c) Exceptions. The obligations of the Receiving Party under Subsection 7.1(b) do not apply to the extent that the Receiving Party can demonstrate that Confidential Information (i) was in the public domain prior to the time of its disclosure under this Agreement; (ii) entered the public domain after the time of its disclosure under this Agreement through means other than an unauthorized disclosure resulting from an act or omission by the Receiving Party; (iii) was already known or independently developed or discovered by the Receiving Party without use of the Confidential Information; (iv) is or was disclosed to the Receiving Party at any time, whether prior to or after the time of its disclosure under this Agreement, by a Third Party having no fiduciary relationship with the Disclosing Party and having no obligation of confidentiality with respect to the Confidential Information; or (v) is required to be disclosed to comply with applicable laws or regulations or with a court or administrative order, provided that the Disclosing Party receives reasonable prior written notice of the disclosure.

(d) Ownership and Return. The Receiving Party acknowledges that the Disclosing Party (or a Third Party entrusting its own information to the Disclosing Party) owns the Confidential Information in the possession of the Receiving Party. Upon expiration or termination of this Agreement, or at the request of the Disclosing Party, the Receiving Party shall return to the Disclosing Party all originals, copies, and summaries of documents, materials, and other tangible manifestations of Confidential Information in the possession or control of the Receiving Party, except that the Receiving Party may retain one copy of the Confidential Information in the possession of its legal counsel solely for the purpose of monitoring its obligations under this Agreement.

7.2 Publicity Restrictions. Neither Isis nor University may use the name of the other party or any of its trustees, officers, directors, faculty, students, employees, or agents, or any adaptation of their names, or any terms of this Agreement in any promotional material or other public announcement or disclosure without the prior written consent of the other party.

8. Term and Termination.

8.1. Term. This Agreement commences on the Effective Date and remains in effect until the expiration of the Royalty Term unless earlier terminated in accordance with the provisions of this Agreement (the "Term").

8.2. Voluntary Termination by Isis. Subject to Subsection 4.6(a), Isis may terminate this Agreement for any reason upon ninety (90) days' prior written notice to University; *provided*, *however*, [***].

8.3. Termination for Default. Subject to Section 3.2, if either party commits a material breach of its obligations under this Agreement and fails to cure that breach within sixty (60) days after receiving written notice of the breach, the other party may terminate this Agreement immediately upon written notice to the party in breach; *provided*, *however*, Isis may not terminate this Agreement during the Royalty Term. If the alleged breach involves nonpayment of any amounts due University under this Agreement, Isis must cure such a material breach within thirty (30) days after receiving written notice of the breach and pay University any applicable interest on such payments under Section 5.6.

8.4 [Reserved]

8.5. Force Majeure. Neither party is responsible for delays resulting from causes beyond its reasonable control, including without limitation fire, earthquake, explosion, flood, war, strike, act of terrorism or riot, provided that the nonperforming party uses commercially reasonable efforts to avoid or remove those causes of nonperformance and continues performance under this Agreement with reasonable dispatch whenever the causes are removed.

8.6. Effect of Termination. The following provisions survive the expiration or termination of this Agreement: Articles 1 and 9; Sections 2.2, 3.3., 3.4, 5.2. (but only to the extent an obligation exists to provide a final report and/or payment), 5.3., 5.4., 5.5., 5.6., 5.7., 5.8., 6.3., 7.1., 7.2, 8.6., 10.9., and 10.10. Upon the early termination of this Agreement, Isis and its Sublicensees may complete and sell any work-in-progress and inventory of Licensed Products that exist as of the effective date of termination, provided that (a) Isis is current in payment of all amounts due University under this Agreement, (b) Isis pays University the applicable royalty and Sublicense Income on sales of Licensed Products in accordance with the terms of this Agreement, and (c) Isis and its Sublicensees complete and sell all work-in-progress and inventory of Licensed Products within six (6) months after the effective date of termination, and pay University royalties on Net Sales of such Licensed Products sold after the effective date of termination in accordance with Section 4.5.

9. Dispute Resolution.

9.1. Procedures Mandatory. Subject to Section 3.2, the parties shall resolve any dispute arising out of or relating to this Agreement solely by means of the procedures set forth in this Article. These procedures constitute legally binding obligations that are an essential provision of this Agreement. If either party fails to observe the procedures of this Article, as modified by their written agreement, the other party may bring an action for specific performance in any court of competent jurisdiction.

9.2. Dispute Resolution Procedures.

(a) Negotiation. In the event of any dispute arising out of or relating to this Agreement, the affected party shall notify the other party, and the parties shall attempt in good faith to resolve the matter within [***] ([***]) days after the date of notice (the "Notice Date"). Any disputes not resolved by good faith discussions shall be referred to senior executives of each party, who shall meet at a mutually acceptable time and location within [***] ([***]) days after the Notice Date and attempt to negotiate a settlement.

(b) Binding Arbitration for Alleged Breach of Commercially Reasonable Efforts.

(i) Any disputes arising between the parties regarding Isis' alleged failure to use Commercially Reasonable Efforts in accordance with Section 3.1(b) will be exclusively determined under this Section 9.2(b) by binding arbitration. All other disputes arising between the parties under this Agreement will be exclusively determined under Section 9.2(c) by mediation and/or Section 9.2(d).

(ii) In the event the designated senior executives are not able to resolve a dispute arising under Section 3.2 regarding Isis' alleged failure to use Commercially Reasonable Efforts during such [***]-day period, then the affected party may initiate arbitration under the procedural arbitration rules of the American Arbitration Association. The venue for the arbitration procedure shall be Boston, Massachusetts, Massachusetts substantive law shall be applied, and the dispute shall be determined by a single arbitrator appointed in accordance with such arbitration rules. Such arbitrator shall be permitted to consider a new Minimum Spend, a new diligence event timeline, and termination of the Agreement in resolving the dispute. The award of the arbitrator shall be the sole and exclusive remedy between the affected parties regarding any such dispute and shall be final and binding upon the parties.

(c) Mediation. If a dispute between the parties is not a matter required to be determined under Section 9.2(b) above, and remains unresolved within [***] ([***]) days after the Notice Date or if the senior executives fail to meet within [***] ([***]) days after the Notice Date, either party may initiate mediation upon written notice to the other party, and both parties shall engage in a mediation proceeding under the then current CPR Institute for Dispute Resolution ("CPR") Model Procedure for Mediation of Business Disputes. Specific provisions of this Subsection 9.2(c) override inconsistent provisions of the CPR Model Procedure. The parties shall select the mediator from the CPR Panels of Neutrals. If the parties cannot agree upon the selection of a mediator within [***] ([***]) days after the Notice Date, then upon the request of either party, the CPR shall appoint the mediator. The parties shall attempt to resolve the dispute through mediation until one of the following occurs: (i) the parties reach a written settlement; (ii) the mediator notifies the parties in writing that they have reached an impasse; (iii) the parties agree in writing that they have reached an impasse; or (iv) the parties have not reached a settlement within [***] ([***]) days after the Notice Date.

(d) Trial Without Jury. If the parties fail to resolve a dispute under Section 9.2(c) through mediation, or if neither party elects to initiate mediation and such dispute is not required to be determined under Section 9.2(b), each party may pursue any other remedies legally available to resolve the dispute. However, the parties expressly waive the right to a jury trial in the legal proceeding under this Subsection 9.2(d).

9.3. Preservation of Rights Pending Resolution.

(a) Performance to Continue. Each party shall continue to perform its obligations under this Agreement pending final resolution of any dispute arising out of or relating to this Agreement. However, a party may suspend performance of its obligations during any period in which the other party fails or refuses to perform its obligations.

(b) Provisional Remedies. Although the procedures specified in this Article are the exclusive procedures for resolution of disputes arising out of or relating to this Agreement, either party may seek a preliminary injunction or other provisional equitable relief if, in its reasonable judgment, that action is necessary to avoid irreparable harm to itself or to preserve its rights under this Agreement.

(c) Statute of Limitations. The parties agree that all applicable statutes of limitation and time-based defenses (such as, estoppel and laches) are tolled while the procedures set forth in Subsections 9.2(a) and 9.2(c) are pending. The parties shall take any actions necessary to effectuate this result.

10. Miscellaneous.

10.1. Representations and Warranties. University represents that its employees have assigned to University their entire right, title, and interest in the Patent Rights, and that it has authority to grant the rights and licenses set forth in this Agreement, and that it has not granted any rights in the Patent Rights to any Third Party that is inconsistent with the grant of rights in this Agreement. UNIVERSITY MAKES NO OTHER WARRANTIES CONCERNING THE PATENT RIGHTS, INCLUDING WITHOUT LIMITATION ANY EXPRESS OR IMPLIED WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. Specifically, University makes no warranty or representation (a) regarding the validity or scope of the Patent Rights, (b) that the exploitation of the Patent Rights or any Licensed Product will not infringe any patents or other intellectual property rights of a Third Party, and (c) that any Third Party is not currently infringing or will not infringe the Patent Rights.

10.2. Compliance with Law. Isis agrees to comply with applicable law and shall promptly notify University of any violation that Isis knows or has reason to believe has occurred or is likely to occur.

10.3. Tax-Exempt Status. University is a public institution of the Commonwealth of Massachusetts, and is an exempt organization under the United States Internal Revenue Code of 1986, as amended. Isis also acknowledges that certain facilities in which the licensed inventions were developed may have been financed through offerings of tax-exempt bonds. If the Internal Revenue Service determines, or if counsel to University reasonably determines that any term of this Agreement jeopardizes the tax-exempt status of University or the bonds used to finance University facilities, the relevant term is invalid and shall be modified in accordance with Section 10.11.

10.4. Counterparts. This Agreement may be executed in one or more counterparts, each of which is an original, and all of which together are one instrument.

10.5. Headings. All headings are for convenience only and do not affect the meaning of any provision of this Agreement.

10.6. Binding Effect. This Agreement is binding upon and inures to the benefit of the parties and their respective permitted successors and assigns.

10.7. Assignment. This Agreement may not be assigned by either party without the prior written consent of the other party, which consent may not be unreasonably withheld or delayed. Notwithstanding the foregoing, this Agreement may be assigned by either party without the prior written consent of the other party to a Third Party in connection with a merger, consolidation, sale of all of the equity interests of the party, or a sale of all or substantially all of the assets of the party to which this Agreement relates.

10.8. Amendment and Waiver. The parties may only amend, supplement, or otherwise modify this Agreement through a written instrument signed by both parties. The waiver of any rights or failure to act in a specific instance relates only to that instance and is not an agreement to waive any rights or fail to act in any other instance.

10.9. Governing Law. This Agreement is governed by and construed in accordance with the laws of the Commonwealth of Massachusetts irrespective of any conflicts of law principles. The parties may only bring legal action that arises out of or in connection with this Agreement in Massachusetts Superior Court in Suffolk County.

10.10. Notice. Any notices required or permitted under this Agreement shall be in writing, shall specifically refer to this Agreement, and shall be sent by recognized national overnight courier, or registered or certified mail, postage prepaid, return receipt requested, to the following addresses:

| **If to University:** | **If to Isis:** |
|---|---|
| Office of Technology Management<br>University of Massachusetts<br>222 Maple Ave., Higgins Building<br>Shrewsbury, MA 01545 | Isis Pharmaceuticals, Inc.<br>1896 Rutherford Road<br>Carlsbad, CA 92008 |
| Attention: Executive Director | Attention: COO & CFO |
| | With a copy to: General Counsel |

All notices under this Agreement are effective upon receipt. A party may change its contact information immediately upon written notice to the other party in the manner provided in this Section 10.10.

10.11. Severability. If any provision of this Agreement is held invalid or unenforceable for any reason, the invalidity or unenforceability does not affect any other provision of this Agreement, and the parties shall negotiate in good faith to modify the Agreement to preserve (to the extent possible) their original intent. If the parties fail to reach a modified agreement within sixty (60) days after the relevant provision is held invalid or unenforceable, then the dispute shall be resolved in accordance with the procedures set forth in Article 9. While the dispute is pending resolution, this Agreement shall be construed as if the provision were deleted by agreement of the parties.

10.12. Entire Agreement. This Agreement constitutes the entire agreement between the parties with respect to its subject matter and supersedes all prior agreements or understandings between the parties relating to its subject matter.

THE PARTIES have caused this Agreement to be executed by their duly authorized representatives as of the Effective Date.

**UNIVERSITY OF MASSACHUSETTS**

By: */s/ James P. McNamara*

Name: James P. McNamara, Ph.D.,
Title: Executive Director,
Office of Technology Management

**ISIS PHARMACEUTICALS, INC.**

By: */s/ B. Lynne Parshall*

Name: B. Lynne Parshall
Title: COO & CFO

**EXHIBIT A**

**Patent Rights**

[***]

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

EXHIBIT 10.2

***Execution Version – Confidential***

# AMENDED AND RESTATED COLLABORATION AND LICENSE AGREEMENT

This Amended and Restated Collaboration and License Agreement ("***Agreement***") is made effective October 26, 2011 (the "***Restatement Date***") and is entered into by and between **COLD SPRING HARBOR LABORATORY**, a research and education institution having an address at One Bungtown Road, Cold Spring Harbor, New York 11724 ("***CSHL***") and **ISIS PHARMACEUTICALS, INC.**, a Delaware corporation having an address at 2855 Gazelle Court, Carlsbad, California 92010 ("***Isis***").

**WHEREAS**, CSHL and Isis have collaborated in the area of modulation of splicing using oligonucleotides, which resulted in joint application [***] (the "***Pre-Existing Joint Patent***");

**WHEREAS**, CSHL and Isis entered into that certain Collaboration and License Agreement dated August 6, 2008 (the "***Original Agreement***") under which (i) CSHL granted to Isis a license to the Collaboration Patents (as defined below), CSHL's interest in the Pre-Existing Joint Patent and any other Joint Patents (as defined below), and (ii) Isis and CSHL entered into a collaboration through the use of Dr. Adrian Krainer's lab at CSHL to further advance the development of the scientific subject matter in the field of splicing under and within the scope of the Research Plan listed in Appendix 2;

**WHEREAS**, Isis and CSHL now desire to amend and restate the Original Agreement in order to (i) modify certain terms of the Original Agreement, and (ii) extend the term and expand the scope of the collaboration as set forth in Appendix 3; and

**NOW, THEREFORE**, for good and valuable consideration, the sufficiency of which is hereby acknowledged, CSHL and Isis hereby agree as follows:

## 1 DEFINITIONS

The terms used in this Agreement with initial letters capitalized, whether used in the singular or the plural, will have the meaning set forth in Appendix 1, or if not listed in Appendix 1, the meaning designated in places throughout the Agreement.

## *2* SCOPE OF LICENSE

**2.1 License Grant.**

**2.1.1 Exclusive License.** Subject to the terms of this Agreement and during the Term, CSHL grants to Isis an exclusive royalty-bearing license under the CSHL Patent Rights to develop, make, have made, use, sell, offer for sale, have sold, import and export Licensed Products in the Territory. This exclusive license is sublicensable.

**2.1.2 Non-Exclusive License.** Subject to the terms of this Agreement and during the Term, CSHL grants to Isis a nonexclusive license under the Enabling Know-How to the extent necessary to make, have made, use, sell and import Licensed Products in the Territory. This non-exclusive license is sublicensable.

**2.2 Information Transfer.** During the Collaboration Term, CSHL will transfer to Isis all Enabling Know-How in CSHL's possession and Control necessary or useful to Isis' exploitation of its rights hereunder with respect to Licensed Products, and will ensure that Isis can transfer (subject to the terms and conditions set forth herein) such Enabling Know-How to Third Parties in connection with the development and/or commercialization of Licensed Products. Where applicable, CSHL may provide only copies and not originals of such Enabling Know How.

**2.3 Sublicenses.**

**2.3.1 Sublicense Requirements.** All sublicenses of the rights granted to Isis under this Agreement (including under Section 2.1.1 and Section 2.1.2) (each, a "***Sublicense***") to Third Parties (each, a "***Sublicensee***") will include all material rights of and obligations due to CSHL under this Agreement, including payment of any applicable royalties and milestone payments on Licensed Products as set forth in Article 4 below. Each Sublicense will provide that CSHL is an intended third party beneficiary of the right to receive royalties (and other obligations) under the Sublicense but only to the extent royalties and milestone payments would be due to CSHL under this Agreement, and Isis will pay such royalties and milestone payments if a Sublicensee fails to do so on time. In addition, Isis has the right to pay directly to CSHL, on a Sublicensee's behalf, any such milestone payments and royalties that become due to CSHL under this Agreement. Isis hereby agrees that under each such Sublicense, the Sublicensee may only further sublicense any of the rights and or licenses under this Agreement to make, have made, use, sell and/or import a Licensed Product. Isis will promptly provide CSHL with the identity of each Sublicensee and a summary of the material financial terms of each Sublicense issued and the Sublicense and the terms of such Sublicense will be treated by CSHL as Confidential Information. Isis will summarize and deliver all reports due CSHL from Sublicensees according to terms consistent with those set forth in Section 4.

**2.3.2** **Sublicense Survival**. If this Agreement terminates for any reason, from the effective date of such termination, any Sublicense granted prior to such termination will survive as a direct license with CSHL and the Sublicensee will automatically become a direct licensee of CSHL with respect to the rights originally sublicensed to the Sublicensee, and Isis agrees that it will confirm the foregoing in writing at the request and for the benefit of CSHL and/or the Sublicensee; *provided*, *however*, that (i) such Sublicensee is not in breach of its Sublicense, (ii) such Sublicensee agrees to comply with all of the terms of this Agreement to the extent applicable to the rights originally sublicensed to such Sublicensee, and (iii) such Sublicensee agrees to pay directly to CSHL such Sublicensee's payments under this Agreement to the extent applicable to the rights sublicensed to such Sublicensee.

**2.4** **Reservation of Rights.** CSHL reserves the right to practice the CSHL Patent Rights for its own noncommercial research purposes.

**2.5** **Government Rights.**The licenses granted to Isis herein are subject to the rights of the US Government as set forth in 37 CFR §401 which is an outgrowth of Public Law 98-620 which amended Public Law 96-517, more commonly known as The Bayh-Dole Act. If there is any conflict between any such rights and the rights granted herein, such Government rights shall prevail.

**2.6** **Covenant Not to Sue.** CSHL covenants, for itself and its Affiliates and successors, not to either directly or indirectly make, file, bring or maintain any claim, demand or lawsuit (a "***Suit***") against Isis, its Affiliates, or Sublicensees (collectively, "***CNTS Parties***"), which Suit asserts that a Licensed Product infringes or misappropriates any of the Enabling Patent Rights. This covenant not to sue is transferable to each of the CNTS Parties and such CNTS Parties are each intended third party beneficiaries of this Section 2.6. For the avoidance of doubt, Enabling Patent Rights will be limited to Patents covering the preparation, manufacture, or use of antisense oligonucleotides for modulating splicing of SMN2 (gene known as survival of motor neuron 2).

**2.7** **Commercially Reasonable Efforts.** Isis and any Sublicensees will use commercially reasonable efforts to develop and commercialize Licensed Products.

## 3 Collaboration Research

**3.1** **Collaboration Research.** The Collaboration Research will be carried out in accordance with a written research plan (the "***Research Plan***"). The initial Research Plan that was agreed to by the Parties as of the Effective Date of the Original Agreement is attached hereto as Appendix 2 and made an integral part of this Agreement. As of the Restatement Date, the Research Plan is updated to include the additional research activities incorporated by the Parties as set forth on Appendix 3 and made an integral part of this Agreement. Within the Krainer Lab, CSHL will use good faith diligent efforts to carry out the research described in the Research Plan. CSHL will ensure that, other than Isis, only the Krainer Lab will perform the research described in the Research Plan. All activities and work performed under the Research Plan will be conducted in a good scientific manner, in compliance with all applicable good laboratory practices, and Applicable Laws.

**3.2 Collaboration Term.** Unless earlier terminated in accordance with this Agreement, the term of the collaboration will commence as of the Effective Date and will continue through October 26, 2013 (the "***Collaboration Term***"). The Parties may extend the Collaboration Term for additional one year periods upon written agreement.

**3.3 Collaboration Records.** CSHL will maintain complete and accurate records of all work it conducts under the Research Plan and any results, data, inventions and developments made under the Research Plan. Such records will be in sufficient detail and in good scientific manner appropriate for Patent and regulatory purposes.

**3.4 Disclosure of Results of Collaboration.** The results of all research performed by CSHL as part of the Collaboration Research will be promptly disclosed to Isis quarterly. On reasonable request by Isis, CSHL will make presentations of its activities under the Research Plan to inform Isis of the details of the work performed. The results, reports, analyses and other information disclosed by CSHL pursuant to this Section 3.4 will only be used by Isis to practice its rights and satisfy its obligations under this Agreement.

**3.5 Collaboration Costs.**

**3.5.1 Isis Funding Under Original Agreement**. The Parties acknowledge that Isis paid CSHL a total of $[***] in funding for the Collaboration Research under the Original Agreement.

**3.5.2 Isis Funding Under this Agreement**. Isis will provide the following additional funding under this Agreement to support the Collaboration Research:

(i) $[***] within [***] days after the Restatement Date;
(ii) $[***] by [***]; and
(iii) $[***] by [***].

Isis will also provide to CSHL certain oligonucleotides necessary for the Collaboration Research and as set forth in the Research Plan, without cost to CSHL. The Parties will otherwise be responsible for and pay their own research costs incurred to perform the Collaboration Research.

**3.6 Management.** The Parties will meet every [***], either in person or by teleconference to discuss research results and to establish research priorities for the Collaboration Research. Isis may, from time to time during the Collaboration Term, make requests to modify the Research Plan. Any such modification will be by written amendment of the Research Plan and will be agreed by both Parties. Also, any such modification which will expand the scope of the existing Research Plan in Appendix 2 or Appendix 3 requires CSHL's consent and the terms of this Agreement may have to be amended accordingly.

**3.7. Exclusivity.** Subject to the obligation(s) under Third Party collaboration(s) or agreements and any grant (including any NIH grant), each of which exists prior to the Effective Date (the "***Prior Agreements***"), during the Collaboration Term, the Krainer Lab at CSHL will not work independently of this Agreement for itself or any Third Party (including the grant of any license to any Third Party) with respect to discovery, research, development and/or commercialization activities with respect to the field of research covered by the Collaboration Research.

**3.8 Termination of Collaboration**. In the event Dr. Adrian Krainer is unable or unwilling to continue to direct and perform the Collaboration Research activities for a period in excess of [***] days, CSHL will notify Isis and may nominate a replacement; if CSHL does not nominate a replacement or if that replacement is unsatisfactory to Isis, Isis may terminate the Collaboration Research upon [***] ([***]) days written notice. For the avoidance of doubt, any such termination of the Collaboration Research (i) is in addition to and exclusive of any other rights and remedies available to Isis, (ii) will terminate Isis' obligation to pay cancellable costs under Section 3.5, and (iii) will in no event terminate this Agreement or the licenses granted hereunder. In the event of such termination by Isis, Isis will still be obligated to pay any non-cancellable amounts due to CSHL hereunder (*e.g.*, non-cancellable supplies purchased for the Collaboration Research) which, but for the lapse of time, will be owed to CSHL.

## 4 License Fees and Royalties; Payments and Reports

**4.1 Fees and Royalties.** Isis will pay to CSHL the fees, milestones and royalties set forth in this Article 4.

**4.1.1 License Fees.** CSHL acknowledges that Isis paid to CSHL, within [***] days after the Effective Date, a non-creditable, non-refundable license fee of $[***] (the "***License Fee***").

**4.1.2 Maintenance Fees.** During the Term, within [***] days after each anniversary of the Effective Date, Isis will pay CSHL a non-creditable, non-refundable annual license maintenance fee equal to $[***].

**4.1.3 Milestones.** During the Term, Isis will pay the following milestones to CSHL within [***] days after achievement of such milestone:

**a.** $[***] upon [***]; *provided, however* that the [***] of the same Licensed Product or Licensed Products that are Modifications of a Licensed Product for which Isis has previously paid CSHL a milestone payment under this Section 4.1.3.a will not trigger an additional milestone payment.

**b.** $[***] for the [***]; *provided, however* that [***] performed on the same Licensed Product or Licensed Products that are Modifications of a Licensed Product for which Isis has previously paid CSHL a milestone payment under this Section 4.1.3.b will not trigger an additional milestone payment.

**c.** $[***] upon [***]; *provided, however* that [***] for the same Licensed Product or Licensed Products that are Modifications of a Licensed Product for which Isis has previously paid CSHL a milestone payment under this Section 4.1.3.c will not trigger an additional milestone payment.

For the avoidance of doubt, each of the above milestones will be payable only once per Licensed Product.

**4.1.4 Royalties on Licensed Products.** During the Term, Isis will pay CSHL a royalty of [***]% on Net Sales of each and any single Licensed Product. Isis will pay CSHL such royalties on Net Sales for Licensed Products until the expiration of the last Valid Claim within the CSHL Patent Rights covering the manufacture, use, or sale of such Licensed Product in such country.

**4.1.5 Third Party Royalty Relief.** If Isis obtains a license from a Third Party that is necessary or useful for the development or commercialization of a Licensed Product or to practice the CSHL Patent Rights ("***Third Party Agreement***"), and such Third Party Agreement requires Isis to pay a royalty to such Third Party (the "***Third Party Royalty***"), the royalty due to CSHL in Section 4.1.4 above will be reduced by an amount equal to [***]% of such Third Party Royalty; *provided, however*, that the royalty to CSHL under Section 4.1.4 above will not be reduced to less than [***]% in any situation after deductions for all such Third Party Royalty.
For example only, if Isis obtains a license under a Third Party Agreement that requires payment of a Third Party Royalty of [***]% on Net Sales of Licensed Products, then the royalty payable to CSHL will be reduced by [***]% (*i.e.*, [***] ([***]) of such [***]% Third Party Royalty) to a total royalty to CSHL of [***]% on Net Sales of Licensed Products.

**4.1.6 Sublicense Revenue Sharing.** During the Term, Isis will pay CSHL [***]% of Sublicense Revenue. Any milestone payments made under Section 4.1.3 for a particular Licensed Product are creditable against any Sublicense Revenue obligations involving Sublicenses of said Licensed Product, or Modifications of said Licensed Product under this Section. For clarity, milestone payments for a Licensed Product are not creditable against Sublicense Revenue obligations involving sublicensing of a different Licensed Product.

**4.2 Payments and Reports.**

**4.2.1 Payment.** Royalty and Sublicense Revenue payments will be due at the end of each calendar quarter beginning with the first commercial sale of a Licensed Product or transaction that gives rise to Sublicense Revenue (each such quarter a "***Reporting Period***") and will be paid within [***] days of the close of each Reporting Period. Each payment will be accompanied by a royalty report of the amount of Sublicense Revenue and Net Sales and all adjustments thereto during such Reporting Period. Each royalty report will cover Isis' most recently completed calendar quarter and will show (a) the gross sales, deductions under Net Sales, and Net Sales of Licensed Products sold by Isis or Sublicensees during the most recently completed calendar quarter, (b) the number of each type of Licensed Product sold, (c) the royalties, in U.S. dollars, payable with respect to the Net Sales, (d) the method used to calculate the royalty, and (e) the exchange rate used, if applicable. Starting after the first commercial sale of a Licensed Product, if no royalties are due under Article 4 during any reporting period, a statement to this effect is required.

**4.2.2** **Mode of Payment.** Isis will make all payments required under this Agreement in U.S. Dollars. When payment is received for monies other than United States dollars the amount due CSHL will first be determined in the foreign currency of the country in which such payment originated and then converted into equivalent United States funds. The exchange rate will be that rate quoted in the Wall Street Journal on the last business day of the Reporting Period. If by law, regulations or fiscal policy of a particular country, remittance of royalties in U.S. Dollars is restricted or forbidden, written notice thereof will promptly be given to CSHL, and payment of the royalty will be made by the deposit thereof in local currency to the credit of CSHL in a recognized banking institution in such country selected by Isis and reasonably acceptable to CSHL. When, in any country, the law or regulations prohibit both the transmittal and deposit of royalties on sales in such country, royalty payments will be suspended for as long as such prohibition is in effect and as soon as such prohibition ceases to be in effect, all royalties that Isis would have been under an obligation to transmit or deposit but for the prohibition will forthwith be deposited or transmitted to the extent allowable. In the event CSHL cannot arrange to have the blocked currency transferred out of the foreign country within [***] ([***]) months after deposit, the Parties will meet to discuss suitable and reasonable alternative methods of reimbursing CSHL.

**4.2.3** **Records Retention.** Isis and its Sublicensees will keep complete and accurate records pertaining to the sale of Licensed Products and covering all transactions from which the Net Sales or Sublicense Revenue are derived for a period of [***] ([***]) months after the year in which such Net Sales or Sublicense Revenue were received, and in sufficient detail to permit CSHL to confirm the accuracy of royalty and Sublicense Revenue calculations hereunder.

**4.2.4** **Audit Request.** No more than once each calendar year and at the written request of CSHL, Isis will permit an independent, certified public accountant appointed by CSHL and not having a conflict-of-interest in auditing Isis, at reasonable times and upon reasonable notice, to examine those records and all other material documents relating to or relevant to Net Sales or Sublicense Revenue in the possession or control of Isis, for a period of [***] ([***]) years after such royalties or Sublicense Revenue have accrued, as may be necessary to: (a) determine the correctness of any report or payment made under this Agreement; or (b) obtain information as to the royalties and Sublicense Revenue payable for any Reporting Period in the case of Isis' failure to report or pay pursuant to this Agreement. Said accountant will not disclose to CSHL any information other than information relating to said reports, royalties, and payments and will disclose such information in a format agreed upon by the Parties that will ensure that no Confidential Information of Isis is disclosed. Results of any such examination will be made available to both Parties. The fees charged by the public accountant conducting the audit will be paid for by CSHL, *provided that*, if the audit determines that the additional royalties and Sublicense Revenue payable by Isis for an audited period exceed [***]% of the royalties and Sublicense Revenue actually paid for such period, then Isis will pay the fees and expenses charged by such accounting firm. If a particular Reporting Period is audited, that same Reported Period may not be audited again.

## 5 INVENTIONS; PATENT PROSECUTION; AND ENFORCEMENT

**5.1 Inventorship.** Inventorship of Collaboration Patents will be determined in accordance with U.S. Patent Law.

**5.2 Patent Prosecution.** Promptly following the Effective Date or, in the case of Collaboration Patents not in existence on the Effective Date, at the earliest date practicable thereafter, CSHL will transfer to Isis copies of all files, materials and documents in CSHL's possession necessary to enable Isis to assume the prosecution and maintenance of Collaboration Patents and the Pre-Existing Joint Patent (collectively, "***Transferred Patents***"). Following Isis' receipt of such files, materials, and documents, Isis will be responsible for timely filing, preparation, and maintenance of Transferred Patents. Isis will pay 100% of the costs associated with preparation, filing and prosecution of Transferred Patents. Isis will have sole responsibility and sole discretion in Patent prosecution decisions for Transferred Patents but Isis will (i) use counsel reasonably acceptable to CSHL, and (ii) will not take any action that would be detrimental to CSHL's interests in the Transferred Patents without CSHL's prior written consent. Isis will copy CSHL on all prosecution correspondence to and from US and foreign Patent offices and promptly provide CSHL with copies of all correspondences and communications regarding the Transferred Patents.

**5.3 Abandoned Patents.** If Isis decides to discontinue the prosecution or maintenance of any Transferred Patent (each an "***Abandoned Patent Right***") entirely or in a particular country (each an "***Abandoned Country***"), it will inform CSHL thereof with sufficient time for CSHL to assume the prosecution or maintenance of such Abandoned Patent Right in such Abandoned Countries, and CSHL may, at its own discretion and with no obligation, assume such prosecution or maintenance of such Abandoned Patent Right in such Abandoned Countries. If CSHL assumes the prosecution and maintenance of an Abandoned Patent Right, then at the time of such assumption, the exclusive license under Section 2.1.1 to practice the Abandoned Patent Right (but not the other CSHL Patent Rights) in the Abandoned Countries (but not any other countries) will be converted into a nonexclusive license (a "***License Conversion***"). In the event of a License Conversion, any royalties that arise under Section 4.1.4 solely as a result of the license to an Abandoned Patent Right will be reduced to [***]% on Net Sales of Licensed Products.

**5.4 Enforcement.**

**5.4.1** Each Party will promptly notify the other Party if it becomes aware of any suspected or actual infringement of the Transferred Patents by any person or Third Party. CSHL will not notify a Third Party of the infringement of any of the Transferred Patents without first obtaining Isis' consent, which consent will not be unreasonably denied. Before notifying a Third Party of the infringement of any of the Transferred Patents, Isis will notify CSHL in writing and will not unreasonably reject the adoption of any comments requested by CSHL.

**5.4.2** During the Term of this Agreement, Isis will have the right, but not the obligation, to prosecute at its own expense any infringements of the Transferred Patents and, in furtherance of such rights, CSHL hereby agrees that Isis may join CSHL as a party plaintiff or defendant, as applicable, in any such suit, or if necessary, prosecute such suit solely in the name of CSHL, without expense to CSHL. Isis will control any such proceeding and CSHL will cooperate with Isis. Isis will hold harmless and indemnify CSHL from and against any order for costs arising without fault of CSHL that may be made against CSHL or Isis in such proceedings. The total cost of any infringement action commenced or defended solely by Isis will be borne by Isis. No settlement, consent judgment or other voluntary final disposition of the suit which may impair the value of the Transferred Patents (including, but not limited to, admitting the invalidity or unenforceability of any Transferred Patents and/or granting a license to any Transferred Patents to the allegedly infringing Third Party) may be entered into without consent of CSHL, which consent will not be unreasonably withheld.

**5.4.3** If within [***] ([***]) months after having been notified of any alleged infringement Isis is unsuccessful in causing the alleged infringer to desist or has not brought and has not been diligently prosecuting an infringement action, or if Isis will notify CSHL at any time prior thereto of its intention not to bring suit against any alleged infringer, then in those events only, CSHL will have the right, but not the obligation to prosecute at its own expense any infringement of the Transferred Patents and, in furtherance of such rights, Isis hereby agrees that CSHL may join Isis as a party plaintiff in any such suit, without expense to Isis. CSHL will control any such proceeding and Isis will cooperate with CSHL at CSHL's expense. CSHL will hold harmless and indemnify Isis from and against any order for costs arising without fault of Isis that may be made against Isis or CSHL in such proceedings. No settlement, consent judgment or other voluntary final disposition of the suit (including, but not limited to, admitting the invalidity or unenforceability of any Transferred Patents and/or granting a license to any Transferred Patents to the allegedly infringing Third Party) may be entered into without the consent of Isis, which consent will not be unreasonably withheld.

**5.4.4** If either party will undertake the enforcement and/or defense of the Transferred Patents by litigation pursuant to Sections 5.4.1 or 5.4.2, any recovery or damages (whether by way of settlement or otherwise) received as a result of any such suit will be applied first in satisfaction of any unreimbursed expenses and legal fees of the Party initiating the proceeding and any fees incurred by the other Party related to such proceeding, and then the remainder will be divided between Parties as follows: (i) as to recoveries based on lost profits, CSHL will receive an amount equal to the royalties it would have received under Article 4 if Isis had earned such profits through the sale of Licensed Products and Isis will retain the balance; and (ii) as to recoveries that result from a judgment for punitive damages, the Party initiating the proceeding will receive [***] percent ([***]%) and the other party will receive [***] percent ([***]%) of recoveries.

## 6. Term and Termination

**6.1** **Term.** The term of this Agreement (the "***Term***") commences upon the Effective Date and, unless earlier terminated in accordance with the provisions of this Article 6, will continue until the expiration of all obligations to pay royalties on all Licensed Products to CSHL.

**6.2** **Termination for Breach.** Notwithstanding anything to the contrary herein, a Party may terminate this Agreement in the event that the other Party (the "***Defaulting Party***") materially breaches its obligations hereunder and fails to cure such breach within [***] ([***]) days of receipt of written notice thereof (which notice will specify the breach in reasonable detail and demand it be cured) (or, if such breach cannot be cured in such [***] ([***])-day period, if the Defaulting Party does not commence and diligently continue (until completed) actions to cure such default); *provided*, *however* that any license granted under this Agreement may not be terminated for a material breach under this Section 6.2 (except for an uncured failure to (i) pay any portion of license fees, milestones, and/or royalties due CSHL under Article 4 that are either undisputed or have been confirmed by a certified public accountant pursuant to Section 4.2.4; or (ii) to provide and maintain payment reports under Article 4) to the extent such license is necessary to make, have made, use and sell a Licensed Product, so long as such Licensed Product has at least reached the First Human Dose stage of development. Nothing in the preceding sentence will be construed as relieving Isis of its obligation to continue to use commercially reasonably efforts to develop and commercialize a Licensed Product. Termination pursuant to this section will not relieve the Defaulting Party from liability and damages to the non-Defaulting Party for default. Waiver by either Party of a single default or a succession of defaults will not deprive such Party of any right to terminate this Agreement arising by reason of a subsequent default.

**6.3** **Termination by Isis.** Notwithstanding anything contained herein to the contrary, Isis has the right to terminate this Agreement at any time in its sole discretion by giving [***] ([***]) days advance written notice to CSHL. In the event of such termination by Isis, Isis will still be obligated to pay any amounts due to CSHL hereunder that accrued prior to such termination, which, but for the lapse of time, will be owed to CSHL.

**6.4** **Effect of Termination.** Upon the termination of this Agreement for any reason, all rights licensed to Isis will revert to CSHL.

**6.5** **Accrued Rights, Surviving Rights and Obligations.** Termination or expiration of this Agreement for any reason will be without prejudice to any rights that will have accrued to the benefit of either Party prior to such termination or expiration. Such termination or expiration will not relieve either Party from obligations that are expressly indicated to survive termination or expiration of this Agreement including, without limitation, Isis' obligation to pay all royalties that will have accrued hereunder prior to termination. Without limiting the foregoing, the Parties' rights and obligations under Sections 2.3, 4.2.3, 4.2.4, 5, 6, 7, 9, 10 and 11 will likewise survive termination or expiration of this Agreement.

**6.6** **Rights in Bankruptcy.** All rights and licenses granted under this Agreement are, for purposes of Section 365(n) of the U.S. Bankruptcy Code (*i.e.*, Title 11 of the U.S. Code) or analogous provisions of Applicable Law outside the United States, licenses of rights to "intellectual property" as defined under Section 101 of the U.S. Bankruptcy Code or analogous provisions of Applicable Law outside the United States. The Parties agree that each Party, as licensee of such rights under this Agreement, will retain and may fully exercise all of its rights and elections under the U.S. Bankruptcy Code or any other provisions of Applicable Law outside the United States that provide similar protection for "intellectual property." The Parties further agree that, in the event of the commencement of a bankruptcy proceeding by or against a Party under the U.S. Bankruptcy Code or analogous provisions of Applicable Law outside the United States, the Party that is not subject to such proceeding will be entitled to a complete duplicate of (or complete access to, as appropriate) such intellectual property and all embodiments of such intellectual property, which, if not already in the non subject Party's possession, will be promptly delivered to it upon the non subject Party's written request therefor. Any agreements supplemental hereto will be deemed to be "agreements supplementary to" this Agreement for purposes of Section 365(n) of the U.S. Bankruptcy Code.

## 7. Indemnification; Statement of Responsibility

**7.1 Isis Indemnity.** Isis agrees to indemnify, hold harmless and defend CSHL, its officers, directors, employees and agents, from and against any and all claims, suits, losses, damages, costs, fees and expenses (collectively, "***Claims***") resulting from or arising out of (a) the development, manufacture, storage, sale or other distribution or any other use of CSHL Patent Rights or Licensed Products by Isis, its Affiliates, Sublicensees, agents and representatives or use by end users and other Third Parties of Licensed Products; or (b) Isis' breach of any representation or warranty herein, *except to the extent* any such Claims arise from CSHL's negligence, intentional misconduct, or breach of this Agreement.

**7.2 Indemnity Procedures.** In all cases where a Party seeks indemnification (the "***Indemnitee***") from the other Party (the "***Indemnitor***") under this Article 7, the Indemnitee will promptly notify the Indemnitor of receipt of any Claim covered by such indemnification obligation and will cooperate fully with the Indemnitor in connection with the investigation and defense of such Claim. The Indemnitor will have the right to control the defense, with counsel of its choice, provided that the Indemnitee will have the right to be represented by advisory counsel at its own expense. Neither Party will settle or dispose of the matter in any manner that could negatively and materially affect the rights or liability of the other Party without the prior written consent of such Party, which will not be unreasonably withheld or delayed.

**7.3 Statement of Responsibility.** As between CSHL and Isis, CSHL agrees to be responsible for any Claims resulting from CSHL's negligence, intentional misconduct, or breach of this Agreement.

## 8. Representations, Warranties and Covenants

**8.1 CSHL Representations and Warranty.** CSHL represents, warrants, and covenants to Isis that:

**(i)** CSHL has the lawful right to grant the licenses made the subject of this Agreement;

**(ii)** Except under the Prior Agreements, CSHL has not granted and will not grant any right or enter into any agreement or understanding that conflicts with its obligations or Isis' rights under this Agreement;

**(iii)** CSHL will perform the research under the Research Plan in a professional manner and in accordance with (1) the standards of care and diligence practiced by recognized organizations in performing research of a similar nature at the time the research under the Research Plan is performed, (2) the terms and conditions of this Agreement, and (3) all Applicable Laws (including applicable good laboratory practice regulations as set forth in 21 C.F.R. Part 58, as amended); and

**(iv)** CSHL's personnel and agents have never been (i) debarred, or (ii) convicted of a crime for which a person can be debarred, under subsection (a) or (b) of 21 U.S.C. § 335a, as amended, and CSHL agrees that it does not now and will not in the future use in any capacity the services of any person debarred under subsection (a) or (b) of 21 U.S.C. § 335a, as amended. If during the term of this Agreement, CSHL or any other person performing research under the Research Plan (i) becomes debarred or disqualified, or (ii) receives notice of an action or threat of an action with respect to debarment or disqualification, CSHL will immediately notify Isis

Except as expressly stated in this section, CSHL makes no other representations of any kind or nature whatsoever. CSHL MAKES NO OTHER WARRANTIES OR REPRESENTATIONS, EXPRESS OR IMPLIED, INCLUDING BUT NOT LIMITED TO, WARRANTIES OF FITNESS FOR A PARTICULAR PURPOSE OR MERCHANTABILITY OR NONINFRINGEMENT REGARDING OR WITH RESPECT TO THE CSHL PATENT RIGHTS. WITHOUT LIMITING THE GENERALITY OF THE FOREGOING, NOTHING IN THIS AGREEMENT WILL BE CONSTRUED AS (A) A WARRANTY OR REPRESENTATION BY CSHL AS TO VALIDITY OR SCOPE OF THE CSHL PATENT RIGHTS OR (B) A WARRANTY OR REPRESENTATION THAT ANYTHING MADE, USED, SOLD OR OTHERWISE DISPOSED OF UNDER THE LICENSE IS OR WILL BE FREE FROM INFRINGEMENT OF THIRD PARTY RIGHTS.

**8.2 Isis Representations and Warranties.** Isis represents and warrants to CSHL that Isis has the power and authority to execute, deliver and perform this Agreement, and this Agreement is a valid and binding obligation of Isis, enforceable in accordance with its terms.

## 9. CONFIDENTIALITY

**9.1 Disclosure and Use Restriction.** Each Party agrees that, for so long as this Agreement is in effect and for a period of [***] years thereafter, a Party (the "***Receiving Party***") receiving Confidential Information of the other Party (the "***Disclosing Party***") will (i) maintain in confidence such Confidential Information, (ii) not disclose such Confidential Information except to the Receiving Party's employees having a need-to-know such Confidential Information, (iii) not disclose such Confidential Information to any Third Party without the prior written consent of the Disclosing Party, except for disclosures expressly permitted by this Agreement, and (iv) not use such Confidential Information for any purpose except those expressly permitted by this Agreement.

**9.2 Authorized Disclosure.** To the extent that it is reasonably necessary or appropriate to satisfy its obligations or exercise its rights under this Agreement, a Party may disclose Confidential Information belonging to the other Party in the following instances:

**(a)** filing or prosecuting Patent applications in accordance with this Agreement;

**(b)** communicating with Regulatory Authorities as necessary for the development or commercialization of a Licensed Product in a country, as required in connection with any filing, application or request for Regulatory Approval; *provided, however*, that reasonable measures will be taken to assure confidential treatment of such information;

**(c)** prosecuting or defending litigation;

**(d)** complying with Applicable Laws and regulations (including, without limitation, the rules and regulations of the Securities and Exchange Commission or any national securities exchange, and compliance with tax laws and regulations) and with judicial process, if (i) in the reasonable opinion of the Receiving Party's counsel, such disclosure is necessary for such compliance and (ii) such disclosure is made in accordance with Section 9.3 or 9.4 as applicable; and

**(e)** disclosure, in connection with the performance of this Agreement and solely on a need-to-know basis, to Affiliates, potential or actual collaborators (including potential Sublicensees), potential or actual investment bankers, investors, lenders, or acquirers, or employees, independent contractors or agents, each of whom prior to disclosure must be bound by written obligations of confidentiality and non-use no less restrictive than the obligations set forth in this Article 9; *provided, however*, that the Receiving Party will remain responsible for any failure by any person or Third Party who receives Confidential Information pursuant to this Article 9 to treat such Confidential Information as required under this Article 9.

If Confidential Information is disclosed in accordance with this Section 9.2, such disclosure will not cause any such information to cease to be Confidential Information except to the extent that such permitted disclosure results in a public disclosure of such information (other than by breach of this Agreement). Where reasonably possible and subject to Sections 9.3 and 9.4, the Receiving Party will notify the Disclosing Party of the Receiving Party's intent to make such disclosure pursuant to clauses (a) through (d) of this Section 9.2 prior to making such disclosure to allow the Disclosing Party adequate time to take whatever action it may deem appropriate to protect the confidentiality of the information.

**9.3 Required Disclosure.** A Receiving Party may disclose Confidential Information pursuant to interrogatories, requests for information or documents, subpoena, civil investigative demand issued by a court or governmental agency or as otherwise required by Law; provided however, that the Receiving Party will notify the Disclosing Party promptly upon receipt thereof, giving (where practicable) the Disclosing Party sufficient advance notice to permit it to oppose, limit or seek confidential treatment for such disclosure, and to file for Patent protection if relevant; and provided, further, that the Receiving Party will furnish only that portion of the Confidential Information which it is advised by counsel is legally required whether or not a protective order or other similar order is obtained by the Disclosing Party.

**9.4 Securities Filings.** In the event either Party proposes to file with the Securities and Exchange Commission or the securities regulators of any state or other jurisdiction a registration statement, periodic report, or any other disclosure document which describes or refers to this Agreement under the Securities Act of 1933, as amended, the Securities Exchange Act, of 1934, as amended, or any other applicable securities Law, the Party will notify the other Party of such intention and will provide such other Party with a copy of relevant portions of the proposed filing not less than 3 Business Days prior to such filing, and will seek to obtain confidential treatment of any information concerning the Agreement that such other Party requests be kept confidential (except to the extent advised by counsel that confidential treatment is not available for such information), and will only disclose Confidential Information which it is advised by counsel is legally required to be disclosed. No such notice will be required under this Section 9.4 if the substance of the description of or reference to this Agreement contained in the proposed filing has been included in any previous filing made by either Party hereunder or otherwise approved by the other Party.

**9.5 Terms of Agreement.** The existence and the terms and conditions of the Agreement that the Parties have not specifically agreed to disclose pursuant to Section 9.3 or Section 9.4 are considered Confidential Information of both Parties. Either Party may disclose such terms to a bona fide potential Sublicensee, investor, investment banker, acquirer, merger partner or other potential financial partner, and their attorneys and agents, provided that each such Third Party is informed of the confidential nature of such information and has entered into a written agreement with the Party requiring such Third Party to keep such information confidential.

**9.6 Injunctive Relief.** The Parties understand and agree that remedies at Law may be inadequate to protect against any breach of any of the provisions of this Article 9 by either Party. Accordingly, each Party is entitled to seek injunctive relief by a court of competent jurisdiction against any action that constitutes a breach of this Article 9.

## 10. Press Releases and Publications

**10.1 Press Releases.** Upon execution of this Agreement, the Parties may issue either a joint press release or separate press releases announcing the existence of this Agreement, in each case in a form and substance agreed to in writing by the Parties. Each Party agrees not to issue any other press release or other public statement disclosing other information relating to this Agreement or the transactions contemplated hereby without the prior written consent of the other Party, which consent will not be unreasonably withheld, delayed or conditioned, *provided however*, that each Party may make disclosures permitted by, and in accordance with, Article 9. Each Party agrees to provide to the other Party a copy of any public announcement regarding this Agreement or the subject matter thereof as soon as reasonably practicable prior to its scheduled release. Except under extraordinary circumstances, each Party will provide the other with an advance copy of any such announcement at least [***] business days prior to its scheduled release. Each Party will have the right to expeditiously review and recommend changes to any such announcement and, except as otherwise permitted by Article 9, the Party whose announcement has been reviewed will remove any information the reviewing Party reasonably deems to be inappropriate for disclosure. The contents of any announcement or similar publicity which has been reviewed and approved by the reviewing Party can be re-released by either Party without a requirement for re-approval.

**10.2 Publication of Research Results.** Consistent with academic custom, either Party will publish or present to the public the results arising out of the Research Plan (the "***Research Results***"), except subject to the prior review and comment by the other Party as follows. A Party that desires to publish will provide the other Party with the opportunity to review any such proposed public disclosure, whether written or oral, (such as an abstract, manuscript or presentation) that contains such Research Results by delivering a copy thereof to the other Party no less than [***] ([***]) days before its intended submission for disclosure. Such Party will have [***] ([***]) days from its receipt of any such proposed disclosure in which to notify the publishing Party in writing of review and comment of the disclosure, such review and comment not to be unreasonably withheld, delayed or conditioned. In the event the reviewing Party requests a delay in the disclosure beyond such [***] ([***]) day period for the filing of a Patent application, the publishing Party agrees not to make the proposed disclosure within [***] days from such delay request.

## 11. MISCELLANEOUS

**11.1 Relationship of the Parties.** It is expressly agreed that Isis and CSHL will be independent contractors and that the relationship between the two Parties will not constitute a partnership, joint venture or agency. Neither Isis nor CSHL will have the authority to make any statements, representations or commitments of any kind, or to take any action, which will be binding on the other, without the prior consent of the other Party.

**11.2 Use of Name.** Except as required by Applicable Law, neither Party will use the name, trade name, trademark or other designation of the other Party (including contraction, abbreviation or simulation of any of the foregoing) in any advertising, publicity or other promotional activity without the prior written approval of the other Party.

**11.3 Successors and Assigns.** Except as otherwise provided herein, this Agreement may not be assigned by a Party without the prior written consent of the other, *provided*, *however*, that either Party may assign this Agreement to any successor by merger or to the purchaser of all or substantially all of its assets provided that the Party will remain liable and responsible for the performance and observance of all of its duties and obligations hereunder. Nothing in this Agreement, express or implied, is intended to confer upon any Party other than the Parties hereto or their respective permitted successors and assigns any rights, remedies, obligations or liabilities under this Agreement.

**11.4 Governing Law.** This Agreement will be governed by and construed under the laws of the State of New York without giving effect to its conflict of laws rules.

**11.5 Counterparts.** This Agreement may be executed in two or more counterparts, each of which will be decreed an original, but all of which together will constitute one and the same instrument.

**11.6 Compliance With Laws.** Both Parties will comply with all Applicable Laws pertaining to the research contemplated under the Research Plan, and the development, testing, manufacture, marketing and import or export of Licensed Products and will, as appropriate, include similar provisions in any Sublicense agreements requiring Sublicensees to do the same.

**11.7 Notices.** Unless otherwise provided, any notice required or permitted under this Agreement will be given in writing and will be deemed effectively given upon personal delivery to the Party to be notified or five (5) days after upon deposit with the United States Post Office by registered or certified mail, postage prepaid or through a major courier (such as Federal Express, DHL or UPS), or sent by facsimile, and addressed to the Party to be notified at the address set forth below.

| | |
|---|---|
| To Isis: | Isis Pharmaceuticals, Inc.<br>2855 Gazelle Court<br>Carlsbad, CA 92010<br>Attn: Chief Operating Officer & CFO<br>Fax: 760-603-4650 |
| with copies to: | General Counsel<br>Fax: 760-268-4922 |
| To CSHL: | Cold Spring Harbor Laboratory<br>Office of Technology Transfer<br>One Bungtown Road<br>Cold Spring Harbor, NY 11724<br>Fax: 516-367-8435<br>Phone: 516-367-8301 |

**11.8 Amendments and Waivers.** Any term of this Agreement may be amended and the observance of any term of this Agreement may be waived (either generally or in a particular instance and either retroactively or prospectively), only with the written consent of CSHL and Isis. The waiver by either of the Parties of any breach of any provision hereof by the other Party will not be construed to be a waiver of any succeeding breach of such provision or a waiver of the provision itself.

**11.9 Severability.** If one or more provisions of this Agreement are held to be unenforceable under applicable law, such provision will be excluded from this Agreement and the balance of the Agreement will be interpreted as if such provision were so excluded and will be enforceable in accordance with its terms.

**11.10 Force Majeure.** No Party will be deemed to be in default of this Agreement to the extent the performance of its obligations or attempts to cure any breach are delayed or prevented by reason of any act of God, war, fire, natural disaster, accident, act of government, or any other cause beyond the reasonable control of such Party, if the Party affected will give prompt notice of any such event to the other Party. In the event of such a force majeure event, the time for performance or cure will be extended for the period equal to the duration of such force majeure event but not in excess of six (6) months.

**11.11 Entire Agreement.** This Agreement is the entire agreement of the Parties with respect to the subject matter hereof, and any previous agreements (including the Original Agreement), discussions or understandings, whether written or oral, are hereby merged herein.

**11.12 Dispute Resolution.** The Parties recognize that disputes may from time to time arise between the Parties during the term of this Agreement. In the event of such a dispute, either Party, by written notice to the other Party, may have such dispute referred to the Parties' respective executive officers designated below or their successors, for attempted resolution by good faith negotiations within [***] days after such notice is received. Said designated officers are as follows:

For Isis: General Counsel
For CSHL: VP, Office of Technology Transfer

If the dispute is not resolved as provided above, the Chief Operating Officer & CFO of Isis and the VP, Office of Technology Transfer of CSHL will meet for attempted resolution by good faith negotiations within [***] days after the expiration of the preceding [***] day period.

In the event the designated executive officers are not able to resolve such dispute after such [***]-day period, each Party may pursue its rights and remedies in law or equity in any court of competent jurisdiction.

IN WITNESS WHEREOF, the Parties have caused this Agreement to be executed as of the Effective Date.

| COLD SPRING HARBOR LABORATORY | ISIS PHARMACEUTICALS, INC. |
|---|---|
| */s/ John Maroney* | */s/ B. Lynne Parshall* |
| Signature | Signature |
| John Maroney | B. Lynne Parshall |
| Name | Name |
| Vice President<br>Office of Technology Transfer<br>Legal Counsel | Chief Operating Officer and<br>Chief Financial Officer |
| Title | Title |

**APPENDIX 1**

**DEFINITIONS**

"***Affiliate***" means any legal entity (such as a corporation, partnership, or limited liability company) that is controlled by Isis, is controlling Isis, or is under common control with Isis. For the purposes of this definition, the term "control" means (i) beneficial ownership of at least fifty percent (50%) of the voting securities of a legal entity with voting securities, or (ii) a fifty percent (50%) or greater interest in the net assets or profits of a legal entity without voting securities, or (iii) possession, directly or indirectly, of the power to elect or direct the management of a legal entity.

"***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 but not limited to any applicable rules, regulations, guidelines, or other requirements of the Regulatory Authorities that may be in effect from time to time, but excluding Patent laws.

"***Collaboration Patents***" means Patents that claim inventions made by Isis or the Krainer Lab or jointly by Isis and the Krainer Lab in the course of activities under the Collaboration Research during the Collaboration Term.

"***Collaboration Research***" means research conducted by the Krainer Lab and/or Isis in accordance with (i) the Original Agreement under the mutually agreed upon written Research Plan attached hereto as Appendix 2, and/or (ii) this Agreement under the mutually agreed upon written Research Plan attached hereto as Appendix 3.

"***Collaboration Term***" has the meaning set forth in Section 3.2.

"***Confidential Information***" means all information and any tangible embodiments thereof provided by or on behalf of the Disclosing Party to the Receiving Party either in connection with the discussions and negotiations pertaining to this Agreement or in the course of performing this Agreement, including data; knowledge; practices; processes; ideas; research plans; engineering designs and drawings; research data; manufacturing processes and techniques; scientific, manufacturing, marketing and business plans; and financial and personnel matters relating to the Disclosing Party or to its present or future products, sales, suppliers, customers, employees, investors or business; regardless of whether any of the foregoing are marked "confidential" or "proprietary" or communicated to the other by the Disclosing Party in oral, written, graphic or electronic form.

Notwithstanding the foregoing, information of a Party will not be deemed Confidential Information for purposes of this Agreement to the extent that the Receiving Party can show by competent proof that such information:

(a) was already known to the Receiving Party or any of its Affiliates, without any obligation to the Disclosing Party to keep it confidential or restricting its use, prior to the time of disclosure to such Receiving Party;

(b) was generally available or known to parties reasonably skilled in the field to which such information pertains, or was otherwise part of the public domain, at the time of its disclosure to the Receiving Party;

(c) became generally available or known to parties reasonably skilled in the field to which such information pertains, or otherwise became part of the public domain, after its disclosure to such Receiving Party through no fault of the Receiving Party;

(d) was disclosed to such Receiving Party or any of its Affiliates by a Third Party lawfully in possession thereof, and was not obtained indirectly or directly from the Disclosing Party or in connection with the Collaboration Research; or

(e) was independently discovered or developed outside of the Collaboration Research by employees or (sub)contractors of the Receiving Party or any of its Affiliates, without the aid, application or use of Confidential Information of the Disclosing Party.

"***Control or Controlled*** " means, with respect to any Patent or other intellectual property right, possession of the right (whether by ownership, license or otherwise), to assign, or grant a license, sublicense or other right to or under, such Patent or right as provided for herein without violating the terms of any agreement or other arrangement.

"***CSHL***" means Cold Spring Harbor Laboratory, a nonprofit research and education institution having an address at One Bungtown Road, Cold Spring Harbor, New York 11724 and any of its Affiliates.

"***CSHL Patent Rights***" means CSHL's interest in any and all Collaboration Patents and CSHL's interest in any and all Joint Patents.

"***Effective Date***" means August 6, 2008.

"***EMEA***" means the European Regulatory Authority known as the European Medicines Agency and any successor agency thereto.

"***Enabling Know How***" means any unpatentable developments, know-how, information, methods, processes, designs, concepts or techniques developed by the Krainer Lab during the Collaboration Term that are necessary to practice the inventions claimed in the CSHL Patent Rights.

"***Enabling Patent Rights***" means those Patents (i) Controlled by CSHL, (ii) having as an inventor Dr. Adrian Krainer and/or a scientist in Dr. Krainer's laboratory under his direct supervision at CSHL at the time the invention claimed in such Patent was invented, and (iii) that were made prior to or during the Collaboration Term and are necessary for Isis to practice the inventions claimed in the CSHL Patent Rights. Enabling Patent Rights will not include inventions not generally described in the body of the CSHL Patent Rights.

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

"***First Human Dose***" means the first time in which a dose of a Licensed Product is administered to a human being.

"***Initiation of a Phase III Clinical Trial***" means the first visit by the first human patient in a Phase III Clinical Trial during which dosing of a Licensed Product or placebo occurs.

"***Isis***" means Isis Pharmaceuticals, Inc., a Delaware Corporation, having offices at 2855 Gazelle Court, Carlsbad, California 92010 and any of its Affiliates.

"***Isis Patents***" means Collaboration Patents that name Isis inventors and not CSHL inventors.

"***Joint Patents***" means (i) the Pre-Existing Joint Patent, and (ii) Collaboration Patents that name at least one Isis inventor and at least one CSHL inventor.

"***Krainer Lab***" means the laboratory of Dr. Adrian Krainer at CSHL, which includes Dr. Adrian Krainer, all scientists, post-doctoral fellows, graduate students, technicians and other personnel performing work in or for such laboratory and/or Dr. Krainer (excluding any Isis personnel).

"***Licensed Product***" means any drug or diagnostic product that cannot be developed, manufactured, used, or sold without infringing one or more Valid Claim of the CSHL Patent Rights in the country in which such drug or diagnostic product is manufactured, used, or sold.

"***Major Market Country***" means the United States, United Kingdom, Germany, or Japan.

"***Modification***" means, with respect to a Licensed Product, a change in such Licensed Product's sequence, chemistry or formulation so long as such Licensed Product modulates the same molecular target in the same therapeutic area.

"***Net Sales***" will mean the gross invoice price of Licensed Product sold for commercial use by Isis, its Affiliates or Sublicensees to a Third Party less the following items: (i) trade discounts, credits or allowances, (ii) credits or allowances additionally granted upon returns, rejections or recalls (except where any such recall arises out of Isis' or Sublicensee's gross negligence, willful misconduct or fraud), (iii) freight, shipping and insurance charges, (iv) taxes, duties or other governmental tariffs (other than income taxes) and (v) government-mandated rebates.

Notwithstanding the foregoing, if (i) Isis enters an arms-length license agreement with a Third Party with respect to a Licensed Product and (ii) the definition of Net Sales is different in such license agreement than as described above, then, the Parties will use the definition described in the Third Party license for the calculation of royalties hereunder; *provided that* Isis uses good faith efforts to endeavor to negotiate with such Third Party a net sales definition that is the same or substantially similar to the definition of "*Net Sales*" in this Agreement.

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

"***Party***" means either CSHL or Isis individually, and the "***Parties***" means both Isis and CSHL together.

"***Patent***" or "***Patents***" means (a) patent applications (including provisional applications and applications for certificates of invention); (b) any patents issuing from such patent applications (including certificates of invention); (c) all patents and patent applications based on, corresponding to, or claiming the priority date(s) of any of the foregoing; and (d) any substitutions, extensions (including supplemental protection certificates), registrations, confirmations, reissues, divisionals, continuations, continuations-in-part (but only to the extent claiming subject matter previously disclosed in the parent application), re-examinations, renewals and foreign counterparts thereof.

"***Phase III Clinical Trial***" means a human clinical trial of a Licensed Product on a sufficient number of subjects that is designed to establish that a pharmaceutical product is safe and efficacious for its intended use, and to determine warnings, precautions, and adverse reactions that are associated with such pharmaceutical product in the dosage range to be prescribed, which trial is intended to support Regulatory Approval of a Licensed Product, as described in 21 C.F.R. 312.21(c) for the United States, or a similar clinical study prescribed by the Regulatory Authorities in a foreign country.

"***Pre-Existing Joint Patent***" means joint application [***], and (a) any patents issuing from such patent application (including certificates of invention); (b) all patents and patent applications based on, corresponding to, or claiming the priority date(s) of any of the foregoing; and (c) any substitutions, extensions (including supplemental protection certificates), registrations, confirmations, reissues, divisionals, continuations, continuations-in-part (but only to the extent claiming subject matter previously disclosed in such joint application [***]), re-examinations, renewals and foreign counterparts thereof.

"***Publication***" means any public disclosure of information related to the CSHL Patent Rights or the subject matter covered by the Research Plan, including manuscripts, presentations, slides, overheads, outlines, summaries, abstracts, and posters.

"***Regulatory Approval***" means, with respect to a Licensed Product in a regulatory jurisdiction, any and all approvals (including any applicable governmental price and reimbursement approvals), licenses, registrations or authorizations of any Regulatory Authority necessary for the manufacture, use, storage, import, promotion, marketing, pricing and/or sale of a pharmaceutical product in a country.

"***Regulatory Authority***" means any federal, national, multinational, state, provincial or local regulatory agency, department, bureau or other governmental entity with authority over the testing, manufacture, use, storage, import, promotion, marketing, pricing and/or sale of a Licensed Product in a country, including the FDA and the EMEA.

"***Research Plan***" has the meaning set forth in Section 3.1.

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

"***Sublicense***" has the meaning set forth in Section 2.3.1.

"***Sublicensee***" has the meaning set forth in Section 2.3.1.

"***Sublicense Revenue***" means any payments that Isis receives from a Sublicensee in consideration of a Sublicense to the rights granted to Isis under Section 2, including, but not limited to, license fees, milestone payments, and license maintenance fees, but excluding the following payments: (i) payments made in consideration for the issuance of equity or debt securities of Isis, (ii) payments specifically committed to reimburse Isis for the cost to develop Licensed Products and (iii) payments associated with the sale of Licensed Products that would count as Net Sales on which a royalty would be due under Section 4.1.4. If Isis receives any non-cash Sublicense Revenue including (i) and (ii) of this paragraph and Isis is permitted to transfer such non-cash Sublicense Revenue to CSHL, then Isis will transfer an appropriate portion (as calculated pursuant to Section 4.1.6) of such non-cash consideration to CSHL. Otherwise, Isis will pay CSHL a cash payment equal to the fair market value of CSHL's appropriate portion of the Sublicense Revenue (as calculated pursuant to Section 4.1.6).

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

"***Third Party***" means any person or legal entity other than CSHL and Isis.

"***Valid Claim***" means (a) in the case of a US or foreign Patent application, a claim that has not been cancelled, withdrawn, or abandoned without being re-filed in another application or that has not been finally rejected by an administrative agency action from which no appeal has been taken or can be taken or (b) in the case of an unexpired US or foreign Patent, a claim that has not been donated to the public, disclaimed, nor held invalid or unenforceable by a court or government agency of competent jurisdiction in an unappealed or unappealable decision, including through opposition, reexamination, reissue or disclaimer; *provided, however,* if a claim of a pending Patent application has not issued as a claim of an issued patent within the CSHL Patent Rights within [***] ([***]) years after the filing date of the patent application, such pending claim will cease to be a Valid Claim for purposes of this Agreement *unless and until* such pending claim becomes an issued claim of an issued patent within the CSHL Patent Rights (at which time it will be deemed a "*Valid Claim*").

## Appendix 2

**Research Plan as of the Effective Date**

[***]

## Appendix 3

### Research Plan as of the Restatement Date

[***]

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

EXHIBIT 10.3

***EXECUTION COPY***

**AMENDMENT TO**
**AMENDED AND RESTATED COLLABORATION AND LICENSE AGREEMENT**
**RELATING TO [***]**

This Agreement ("***Agreement***") is made effective March 14, 2014 and is entered into by and between **COLD SPRING HARBOR LABORATORY**, a research and education institution having an address at One Bungtown Road, Cold Spring Harbor, New York 11724 ("***CSHL***") and **ISIS PHARMACEUTICALS, INC.**, a Delaware corporation having an address at 2855 Gazelle Court, Carlsbad, California 92010 ("***Isis***").

**WHEREAS**, Isis and CSHL are parties to the Amended and Restated Collaboration and License Agreement dated October 26, 2011 (the ***"Collaboration Agreement"***);

**WHEREAS,** CSHL and Isis [***];

**WHEREAS,** on March 14, 2014, [***]; and

**WHEREAS**, [***], Isis and CSHL now desire to amend certain terms of the Collaboration Agreement solely with respect to the [***], including [***] development and commercialization of Licensed Products thereunder;

**NOW, THEREFORE**, for good and valuable consideration, the sufficiency of which is hereby acknowledged, Isis and CSHL hereby agree as follows:

**1 [***].** Isis will make an [***] to CSHL in the amount of [***] dollars (US $[***]) by wire transfer no later than the close of business on April 14, 2014.

**2 [***].** CSHL will [***], including but not limited to the [***], and the [***].

**3 AMENDMENT TO THIRD PARTY ROYALTY RELIEF.** Solely with respect to the [***], Section 4.1.5 of the Collaboration Agreement is replaced with the following:

**"4.1.5 Third Party Royalty Relief.** If Isis obtains a license from a Third Party that is necessary or useful for the development or commercialization of a Licensed Product or to practice the CSHL Patent Rights ("***Third Party Agreement***"), and such Third Party Agreement requires Isis to pay a royalty to such Third Party (the "***Third Party Royalty***"), the royalty due to CSHL in Section 4.1.4 above will be reduced by an amount equal to [***]% of such Third Party Royalty; *provided*, *however*, that the royalty to CSHL under Section 4.1.4 above will not be reduced to less than [***]% on Net Sales in any situation after deductions for all such Third Party Royalty.

For example only, if Isis obtains a license under a Third Party Agreement that requires payment of a Third Party Royalty of [***]% on Net Sales of Licensed Products, then the royalty payable to CSHL will be reduced by [***]% (*i.e.*, [***] ([***]) of such [***]% Third Party Royalty) to a total royalty to CSHL of [***]% on Net Sales of Licensed Products.

For further example, if Isis obtains a license under a Third Party Agreement that requires payment of a Third Party Royalty of [***]% on Net Sales of Licensed Products, then the royalty payable to CSHL will be reduced by [***]% (*i.e.*, [***] ([***]) of such [***]% Third Party Royalty but subject to the [***]% minimum) to a total royalty to CSHL of [***]% on Net Sales of Licensed Products."

**4 SUBLICENSE REVENUE SHARING [***]**

**4.1 Sublicense Revenue Sharing.** Isis' obligations to pay CSHL Sublicense Revenue sharing payments under Section 4.1.6 of the Collaboration Agreement as a result of the [***] will be to pay CSHL [***]% of the [***] ([***]) and the [***] for achievement of [***] ([***]) received from [***].

Payment of [***]% of the [***] will be due to CSHL within [***] days of the end of the calendar quarter in which [***], and [***]% of each [***] for achievement of [***] will be due to CSHL within [***] days of the end of the calendar quarter in which the [***] was achieved.

The [***] and [***] for achievement of [***] pursuant to the terms of the [***] in effect as of the date hereof, and the corresponding [***]% payments from Isis to CSHL, are set forth in the following table:

| **Payment Event Pursuant to [***]** | **Payment to Isis from [***]** | **Corresponding [***]% payment from Isis to CSHL** |
|---|---|---|
| [***] | $[***] | $[***] |
| [***] | $[***] | $[***] |
| [***] | $[***] | $[***] |
| [***] | $[***] | $[***] |

**4.2 Credit Against [***].** Only the $[***] milestone payment that is payable by Isis to CSHL pursuant to Section 4.1.3(c) of the Collaboration Agreement will be creditable against the above referenced [***]% payments for achievement of [***].

**4.3 Adjustments to [***] or [***].** If based on clinical data or added requirements for marketing approval by regulatory authorities [***] and Isis adjust the [***] or the [***] for achievement of [***], then Isis will pay CSHL [***]% of such adjusted amounts; *unless* (i) in the case where the sum of such adjusted [***] and [***] for achievement of [***] exceeds $[***], Isis and [***] also decrease payments to Isis pursuant to any other financial provisions of the [***]; or (ii) in the case where the sum of such adjusted [***] and [***] for achievement of [***] is less than or equal to $[***], Isis and [***] also increase payments to Isis pursuant to any other financial provisions of the [***]. In the case of (i) or (ii) above, Isis will pay CSHL [***]% of the [***] and [***] for achievement of [***] set forth in [***] in effect as of the date hereof (with [***]% of the [***] being due to CSHL within [***] days of the end of the calendar quarter in which [***], and [***]% of each [***] for achievement of [***] being due to CSHL within [***] days of the end of the calendar quarter in which the [***]).

**5. ACQUISITIONOF ISIS BY [***] PRIOR TO [***]**. If [***] Acquires Isis and files a [***] without having paid Isis the [***] under [***] then the $[***] payment that otherwise would have been paid to CSHL on [***] will become due and payable. For purposes of this Section 5 of this Agreement, ***"[***] Acquires Isis"*** means (a) a merger or consolidation of Isis with a [***] Entity which results in Isis' voting securities outstanding immediately prior thereto ceasing to represent more than 50% of the combined voting power of the surviving entity immediately after such merger or consolidation, (b) a transaction or series of related transactions in which a [***] Entity becomes the owner of more than 50% of Isis' combined voting power, or (c) the sale or other transfer to a [***] Entity of all or substantially all of Isis' assets. For purposes of this Section 5 of this Agreement, ***"[***] Entity"*** means [***], a Delaware corporation, and any legal entity (such as a corporation, partnership, or limited liability company) that [***] (i) beneficially owns at least fifty percent (50%) of the voting securities of such entity if such entity has voting securities, or (ii) has a fifty percent (50%) or greater interest in the net assets or profits of such entity if such entity does not have voting securities.

**6. EFFECT OF AGREEMENT**. This Agreement applies only to the payments received by Isis from [***] pursuant to the [***]. Except as otherwise expressly amended by this Agreement, the Collaboration Agreement remains unchanged and in full force and effect in accordance with its terms. Defined terms set out in the Collaboration Agreement will have the same meaning in this Agreement, which in each case are incorporated herein by reference, unless otherwise explicitly provided by this Agreement. This Agreement replaces and supersedes the letter dated March 14, 2014 signed by the Parties.

[Signature Page to Follow]

IN WITNESS WHEREOF, the Parties have caused this Agreement to be executed and effective as of March 14, 2014.

| COLD SPRING HARBOR LABORATORY | ISIS PHARMACEUTICALS, INC. |
|---|---|
| */s/ Bruce Stillman* | */s/ B. Lynne Parshall* |
| Signature | Signature |
| Bruce Stillman | B. Lynne Parshall |
| Name | Name |
| President and CEO | Chief Operating Officer |
| Title | Title |

**EXHIBIT 31.1**

**CERTIFICATION**

I, Stanley T. Crooke, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Isis Pharmaceuticals, Inc.;

2. Based on my knowledge, this quarterly report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this quarterly report;

3. Based on my knowledge, the condensed consolidated financial statements, and other financial information included in this quarterly report, fairly present in all material respects the financial condition, condensed consolidated results of operations and condensed consolidated cash flows of the registrant as of, and for, the periods presented in this quarterly report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: November 7, 2014

/s/ Stanley T. Crooke

Stanley T. Crooke, M.D., Ph.D.
*Chief Executive Officer*

**EXHIBIT 31.2**

**CERTIFICATION**

I, Elizabeth L. Hougen, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Isis Pharmaceuticals, Inc.;

2. Based on my knowledge, this quarterly report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this quarterly report;

3. Based on my knowledge, the condensed consolidated financial statements, and other financial information included in this quarterly report, fairly present in all material respects the financial condition, condensed consolidated results of operations and condensed consolidated cash flows of the registrant as of, and for, the periods presented in this quarterly report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: November 7, 2014

/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, 2014, to which this Certification is attached as Exhibit 32.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

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

Dated: November 7, 2014

| /s/ Stanley T. Crooke | /s/ Elizabeth L. Hougen |
|---|---|
| Stanley T. Crooke, M.D., Ph.D. | Elizabeth L. Hougen |
| Chief Executive Officer | Chief Financial Officer |

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