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# UNITED STATES
# SECURITIES AND EXCHANGE COMMISSION

**Washington, DC 20549**

# Form 10-Q

**(Mark One)**

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

**For the Quarterly Period Ended June 30, 2013**

**OR**

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

**For the transition period from to**

**Commission file number 0-19125**

# Isis Pharmaceuticals, Inc.

(Exact name of Registrant as specified in its charter)

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

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

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

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

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

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

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

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

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

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

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

The number of shares of voting common stock outstanding as of August 1, 2013 was 115,307,756.

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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 trademark of Genzyme Corporation**



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

| | June 30, 2013 (Unaudited) | December 31, 2012 |
|---|---|---|
| **ASSETS** | | |
| Current assets: | | |
| Cash and cash equivalents | $ 296,540 | $ 124,482 |
| Short-term investments | 294,212 | 249,964 |
| Contracts receivable | 2,024 | 522 |
| Inventories | 8,309 | 6,121 |
| Investment in Regulus Therapeutics Inc. | 62,190 | 33,622 |
| Other current assets | 5,786 | 8,727 |
| Total current assets | 669,061 | 423,438 |
| Property, plant and equipment, net | 88,312 | 91,084 |
| Licenses, net | 5,528 | 6,579 |

| | | |
|---|---|---|
| Patents, net | 20,149 | 18,646 |
| Deposits and other assets | 5,601 | 5,939 |
| Total assets | $ 788,651 | $ 545,686 |
| | | |
| **LIABILITIES AND STOCKHOLDERS' EQUITY** | | |
| Current liabilities: | | |
| Accounts payable | $ 9,461 | $ 10,239 |
| Accrued compensation | 7,031 | 7,878 |
| Accrued liabilities | 16,514 | 15,401 |
| Accrued income taxes | 8,727 | — |
| Current portion of long-term obligations | 4,853 | 4,879 |
| Current portion of deferred contract revenue | 40,409 | 35,925 |
| Total current liabilities | 86,995 | 74,322 |
| Long-term deferred contract revenue | 75,184 | 66,656 |
| 2 3/4 percent convertible senior notes | 147,099 | 143,990 |
| Long-term obligations, less current portion | 7,382 | 7,402 |
| Long-term financing liability for leased facility | 70,910 | 70,550 |
| Total liabilities | 387,570 | 362,920 |
| Stockholders' equity: | | |
| Common stock, $0.001 par value; 200,000,000 shares authorized, 114,291,999 and 101,481,134 shares issued and outstanding at June 30, 2013 and December 31, 2012, respectively | 114 | 102 |
| Additional paid-in capital | 1,292,745 | 1,077,150 |
| Accumulated other comprehensive gain | 26,986 | 12,480 |
| Accumulated deficit | (918,764) | (906,966) |
| Total stockholders' equity | 401,081 | 182,766 |
| Total liabilities and stockholders' equity | $ 788,651 | $ 545,686 |

See accompanying notes.



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

| | Three Months Ended June 30, | | Six Months Ended June 30, | |
|---|---|---|---|---|
| | 2013 | 2012 | 2013 | 2012 |
| Revenue: | | | | |
| Research and development revenue under collaborative agreements | $ 37,615 | $ 47,140 | $ 79,535 | $ 68,957 |
| Licensing and royalty revenue | 477 | 200 | 1,916 | 1,618 |
| Total revenue | 38,092 | 47,340 | 81,451 | 70,575 |
| | | | | |
| Expenses: | | | | |
| Research and development | 42,631 | 40,435 | 80,944 | 79,149 |
| General and administrative | 3,389 | 3,209 | 6,811 | 6,185 |
| Total operating expenses | 46,020 | 43,644 | 87,755 | 85,334 |
| | | | | |
| Income (loss) from operations | (7,928) | 3,696 | (6,304) | (14,759) |
| | | | | |
| Other income (expense): | | | | |
| Equity in net loss of Regulus Therapeutics Inc. | — | (163) | — | (1,139) |
| Investment income | 589 | 477 | 967 | 1,077 |
| Interest expense | (4,808) | (5,219) | (9,603) | (10,398) |
| Gain on investments, net | 840 | 2 | 1,898 | 19 |
| | | | | |
| Loss before income tax benefit (expense) | (11,307) | (1,207) | (13,042) | (25,200) |
| | | | | |
| Income tax benefit (expense) | 1,181 | — | 1,244 | (2) |
| | | | | |
| Net loss | $ (10,126) | $ (1,207) | $ (11,798) | $ (25,202) |
| | | | | |
| Basic and diluted net loss per share | $ (0.09) | $ (0.01) | $ (0.11) | $ (0.25) |
| Shares used in computing basic and diluted net loss per share | 108,539 | 100,213 | 105,225 | 100,185 |

See accompanying notes.

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

| | Three Months Ended June 30, | | Six Months Ended June 30, | |
|---|---|---|---|---|
| | 2013 | 2012 | 2013 | 2012 |
| Net loss | $ (10,126) | $ (1,207) | $ (11,798) | $ (25,202) |
| Unrealized gains on securities, net of tax | 9,202 | 1,210 | 15,669 | 1,738 |
| Reclassification adjustment for realized gain on the sale of Sarepta shares included in net loss | — | — | (1,163) | — |
| Comprehensive income (loss) | $ (924) | $ 3 | $ 2,708 | $ (23,464) |

See accompanying notes.



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

| | Six Months Ended June 30, | |
|---|---|---|
| | 2013 | 2012 |
| Net cash provided by (used in) operating activities | $ 12,164 | $ (9,288) |
| **Investing activities:** | | |
| Purchases of short-term investments | (144,250) | (116,653) |
| Proceeds from the sale of short-term investments | 96,926 | 142,681 |
| Purchases of property, plant and equipment | (591) | (864) |
| Acquisition of licenses and other assets, net | (1,171) | (1,592) |
| Proceeds from sale of strategic investments | 1,938 | — |
| Net cash (used in) provided by investing activities | (47,148) | 23,572 |
| **Financing activities:** | | |
| Proceeds from equity awards | 36,879 | 1,617 |
| Net proceeds from public common stock offering | 173,223 | — |
| Proceeds from equipment financing arrangement | 2,513 | 9,100 |
| Principal payments on debt and capital lease obligations | (5,573) | (4,833) |
| Net cash provided by financing activities | 207,042 | 5,884 |
| Net increase in cash and cash equivalents | 172,058 | 20,168 |
| Cash and cash equivalents at beginning of period | 124,482 | 65,477 |
| Cash and cash equivalents at end of period | $ 296,540 | $ 85,645 |
| **Supplemental disclosures of cash flow information:** | | |
| Interest paid | $ 2,977 | $ 2,275 |
| Income taxes paid | $ 2 | $ — |
| **Supplemental disclosures of non-cash investing and financing activities:** | | |
| Amounts accrued for capital and patent expenditures | $ 1,055 | $ 679 |

See accompanying notes.



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**ISIS PHARMACEUTICALS, INC.**
**NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS**
**June 30, 2013**
**(Unaudited)**

**1. Basis of Presentation**

The unaudited interim condensed consolidated financial statements for the three and six month periods ended June 30, 2013 and 2012 have been prepared on the same basis as the audited financial statements for the year ended December 31, 2012. The financial statements include all normal recurring adjustments, which we consider necessary for a fair presentation of our financial position at such dates and our operating results and cash flows for those periods. Results for the interim periods are not necessarily indicative of the results for the entire year. For more complete financial information, these financial statements, and notes thereto, should be read in conjunction with the audited financial statements for the year ended December 31, 2012 included in our Annual Report on Form 10-K filed with the Securities and Exchange Commission ("SEC").

The condensed consolidated financial statements include the accounts of Isis Pharmaceuticals, Inc. ("we", "us" or "our") and our wholly owned subsidiary, Symphony GenIsis, Inc., which is currently inactive. In addition to our wholly owned subsidiary, our condensed consolidated financial statements include our equity investment in Regulus Therapeutics Inc. In October 2012, Regulus completed an initial public offering (IPO). We now own less than 20 percent of Regulus' common stock and we no longer have significant influence over the operating and financial policies of Regulus. As a result, in the fourth quarter of 2012, we stopped using the equity method of accounting for our equity investment in Regulus and we began accounting for our investment at fair value.

## 2. Significant Accounting Policies

**Revenue Recognition**

We generally recognize revenue when we have satisfied all contractual obligations and are reasonably assured of collecting the resulting receivable. We are often entitled to bill our customers and receive payment from our customers in advance of recognizing the revenue. In those instances in which we have received payment from our customers in advance of recognizing revenue, we include the amounts in deferred revenue on our condensed consolidated balance sheet.

*Research and development revenue under collaborative agreements*

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

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





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

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

We determined that the initial allocable arrangement consideration was the $25 million upfront payment because it was the only payment that was fixed and determinable when we entered into the agreement. In June 2013, we increased the allocable consideration to $31 million when we received the $6 million payment. There was considerable uncertainty at the date of the agreement as to whether we would earn the milestone payments, royalty payments,

payments for manufacturing clinical trial materials or payments for finished drug product. As such, we did not include those payments in the allocable consideration.

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

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

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

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

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



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Typically, we must estimate our period of performance when the agreements we enter into do not clearly define such information. Our collaborative agreements typically include a research and/or development project plan that includes the activities the agreement requires each party to perform during the collaboration. We estimate the period of time over which we will complete the activities for which we are responsible and use that period of time as our period of performance for purposes of revenue recognition and amortize revenue over such period. If our collaborators ask us to continue performing work in a collaboration beyond the initial period of performance, we extend our amortization period to correspond to the new extended period of performance. The revenue we recognize could be materially different if different estimates prevail.

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

In January 2012, we entered into a collaboration agreement with Biogen Idec to develop and commercialize ISIS-SMN$_{Rx}$ for Spinal Muscular Atrophy, or SMA. As part of the collaboration, we received a $29 million upfront payment and we are responsible for global development of ISIS-SMN$_{Rx}$ through completion of Phase 2/3 clinical trials. In June 2012, we entered into a second and separate collaboration agreement with Biogen Idec to develop and commercialize a novel antisense drug targeting DMPK, or dystrophia myotonica-protein kinase. As part of the collaboration, we received a $12 million upfront payment and we are responsible for global development of the drug through the completion of a Phase 2 clinical trial. In December 2012, we entered into a third and separate collaboration agreement with Biogen Idec to discover and develop antisense drugs against three targets to treat neurological or neuromuscular disorders. As part of the collaboration, we received a $30 million upfront payment and we are responsible for the discovery of a lead antisense drug for each of three targets. All three 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 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 the SMA, DMPK, and neurology agreements to determine whether we should account for them as separate agreements or as a single multiple element arrangement. We determined that we should account for the agreements separately because we conducted the negotiations independently of one another, the first two agreements cover two different diseases while the targets for the third agreement were not defined at the inception of the agreement, 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 three of these agreements, we determined that the options did not have stand-alone value because Biogen Idec cannot pursue the development or commercialization of the drugs resulting from these collaborations until it exercises the respective option or options. As such, for each agreement we considered the deliverables to be a single unit of accounting and we are recognizing the upfront payment for each of the agreements over the respective research and development term, which is the estimated period of our performance.

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

in the following paragraph.

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



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candidate is safe based on the Phase 1 data, we or our partners initiate Phase 2 studies that are generally larger scale studies in patients with the primary intent of determining the efficacy of the development candidate. The final step in the development stage is Phase 3 studies to gather the necessary safety and efficacy data to request marketing approval from the Food and Drug Administration, or FDA, and/or foreign equivalents. The Phase 3 studies typically involve large numbers of patients and can take up to several years to complete. If the data gathered during the trials demonstrates acceptable safety and efficacy results, we or our partner will submit an application to the FDA and/or its foreign equivalents for marketing approval. This stage of the drug's life-cycle is the regulatory stage. If a drug achieves marketing approval, it moves into the commercialization stage, during which our partner will market and sell the drug to patients. Although our partner will ultimately be responsible for marketing and selling the drug, our efforts to discover and develop a drug that is safe, effective and reliable contributes significantly to our partner's ability to successfully sell the drug. The FDA and its foreign equivalents have the authority to impose significant restrictions on an approved drug through the product label and on advertising, promotional and distribution activities. Therefore, our efforts designing and executing the necessary animal and human studies are critical to obtaining claims in the product label from the regulatory agencies that would allow our partner to successfully commercialize our drug. Further, the patent protection afforded our drugs as a result of our initial patent applications and related prosecution activities in the United States and foreign jurisdictions are critical to our partner's ability to sell our drugs without competition from generic drugs. The potential sales volume of an approved drug is dependent on several factors including the size of the patient population, market penetration of the drug, and the price charged for the drug.

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

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

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

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

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

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

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

We assess whether a substantive milestone exists at the inception of our agreements. When a substantive milestone is achieved, we recognize revenue related to the milestone payment. For our existing licensing and collaboration agreements in which we are involved in the discovery and/or development of the related drug or provide the partner with ongoing access to new technologies we discover, we have determined that all future development, regulatory and commercialization milestones are substantive. For example, for our strategic alliance with GlaxoSmithKline, or GSK, we are using our antisense drug discovery platform to seek out and develop new drugs against targets for rare and serious diseases. Alternatively, we provide on-going access to our technology to Alnylam Pharmaceuticals, Inc. to develop and commercialize RNA interference, or RNAi, therapeutics. We consider milestones for both of these collaborations to be substantive. For those agreements that do not meet the following criteria, we do not consider the future milestones to be substantive. In evaluating if a milestone is substantive we consider whether:



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- Substantive uncertainty exists as to the achievement of the milestone event at the inception of the arrangement;
- The achievement of the milestone involves substantive effort and can only be achieved based in whole or part on our performance or the occurrence of a specific outcome resulting from our performance;

- The amount of the milestone payment appears reasonable either in relation to the effort expended or to the enhancement of the value of the delivered items;
- There is no future performance required to earn the milestone; and
- The consideration is reasonable relative to all deliverables and payment terms in the arrangement.

If any of these conditions are not met, we will defer recognition of the milestone payment and recognize it as revenue over the estimated period of performance, if any. We earned $46 million in milestone payments in the first half of 2013, including a $25 million milestone payment from Genzyme we recognized in the first quarter of 2013 when the FDA approved the KYNAMRO NDA. We consider milestone payments related to progression of a drug through the development and regulatory stages of its life cycle to be substantive milestones because the level of effort and inherent risk associated with these events is high. Therefore, we recognized the entire $46 million in milestone payments in the first half of 2013. Further information about our collaborative arrangements can be found in Note 8, *Collaborative Arrangements and Licensing Agreements*, below and Note 7, *Collaborative Arrangements and Licensing Agreements*, of our audited financial statements for the year ended December 31, 2012 included in our Annual Report on Form 10-K filed with the SEC.

*Licensing and royalty revenue*

We often enter into agreements to license our proprietary patent rights on an exclusive or non-exclusive basis in exchange for license fees and/or royalties. We generally recognize as revenue immediately those licensing fees and royalties for which we have no significant future performance obligations and are reasonably assured of collecting the resulting receivable.

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

We consider all liquid investments with maturities of 90 days or less when we purchase them to be cash equivalents. Our short-term investments have initial maturities of greater than 90 days from date of purchase. We classify our short-term investments as “available-for-sale” and carry them at fair market value based upon prices for identical or similar items on the last day of the fiscal period. We record unrealized gains and losses as a separate component of comprehensive income (loss) and include net realized gains and losses in gain (loss) on investments. We use the specific identification method to determine the cost of securities sold.

We have equity investments in privately- and publicly-held biotechnology companies that we have received as part of a technology license or collaboration agreement. At June 30, 2013 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. The cost method investments we hold are in early stage biotechnology companies and realization of our equity position in those companies is uncertain. In those circumstances we record a full valuation allowance. In determining if and when a decrease in market value below our cost in our equity positions is temporary or other-than-temporary, we examine historical trends in the stock price, the financial condition of the company, near term prospects of the company and our current need for cash. If we determine that a decline in value in either a public or private investment is other-than-temporary, we recognize an impairment loss in the period in which the other-than-temporary decline occurs.

**Inventory valuation**

We capitalize the costs of raw materials that we purchase for use in producing our drugs because until we use these raw materials they have alternative future uses. We include in inventory raw material costs for drugs that we manufacture for our partners under contractual terms and that we use primarily in our clinical development activities and drug products. We can use each of our raw materials in multiple products and, as a result, each raw material has future economic value independent of the development status of any single drug. For example, if one of our drugs failed, we could use the raw materials for that drug to manufacture our other drugs. We expense these costs when we deliver the drugs to our partners, or as we provide these drugs for our own clinical trials. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. We review inventory periodically and reduce the carrying value of items we consider to be slow moving or obsolete to their estimated net realizable value. We consider several factors in estimating the net realizable value, including shelf life of raw materials, alternative uses for our drugs and clinical trial materials and historical write-offs. We did not record any inventory write-offs for the first six months of 2013 and 2012. Total inventory, which consisted of raw materials, was $8.3 million and $6.1 million as of June 30, 2013 and December 31, 2012, respectively.



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**Patents**

We capitalize costs consisting principally of outside legal costs and filing fees related to obtaining patents. We review our capitalized patent costs regularly to ensure that they include costs for patents and patent applications that have future value. We evaluate patents and patent applications that we are not actively pursuing and write off any associated costs. We amortize patent costs over their useful lives, beginning with the date the United States Patent and Trademark Office, or foreign equivalent, issues the patent. For the first six months of 2013 and 2012, we recorded non-cash charges of $275,000 and $288,000, respectively, which we included in research and development expenses, related to the write-down of our patent costs to their estimated net realizable values.

**Long-lived assets**

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

**Equity method of accounting**

We accounted for our ownership interest in Regulus using the equity method of accounting until Regulus’ IPO in October 2012. In the fourth quarter of 2012, we began accounting for our investment at fair value because we now own less than 20 percent of Regulus’ common stock and we no longer have

significant influence over the operating and financial policies of Regulus. Under the equity method of accounting, we included our share of Regulus' operating results on a separate line in our condensed consolidated statement of operations called "Equity in net loss of Regulus Therapeutics Inc."

**Use of estimates**

The preparation of condensed consolidated financial statements in conformity with accounting principles generally accepted in the United States requires management to make estimates and assumptions that affect the amounts reported in the condensed consolidated financial statements and accompanying notes. Actual results could differ from those estimates.

**Basic and diluted net loss per share**

We compute basic net loss per share by dividing the net loss by the weighted-average number of common shares outstanding during the period. As we incurred a net loss for the three and six months ended June 30, 2013 and 2012, we did not include dilutive common equivalent shares in the computation of diluted net loss per share because the effect would have been anti-dilutive. The following would have had an anti-dilutive effect on net loss per share:

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

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

**Public Common Stock Offering**

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



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**Consolidation of variable interest entities**

We identify entities as variable interest entities either: (1) that do not have sufficient equity investment at risk to permit the entity to finance its activities without additional subordinated financial support, or (2) in which the equity investors lack an essential characteristic of a controlling financial interest. We perform ongoing qualitative assessments of our variable interest entities to determine whether we have a controlling financial interest in the variable interest entity and therefore are the primary beneficiary. As of June 30, 2013 and December 31, 2012, we had collaborative arrangements with five and six entities, respectively, that we considered to be variable interest entities. We are not the primary beneficiary for any of these entities as we do not have both the power to direct the activities that most significantly impact the economic performance of our variable interest entities and the obligation to absorb losses or the right to receive benefits from our variable interest entities that could potentially be significant to the variable interest entities. As of June 30, 2013, the total carrying value of our investments in variable interest entities was $63.6 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 (loss)**

Accumulated other comprehensive income (loss) 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 (loss) for the three and six months ended June 30, 2013 and 2012 (in thousands):

| | Three Months Ended June 30, | | Six Months Ended June 30, | |
|---|---|---|---|---|
| | 2013 | 2012 | 2013 | 2012 |
| Beginning balance accumulated other comprehensive income (loss) | $ 17,784 | $ (242) | $ 12,480 | $ (770) |
| Other comprehensive income before reclassifications, net of tax (1) | 9,202 | 1,210 | 15,669 | 1,738 |
| Amounts reclassified from accumulated other comprehensive income (2) | — | — | (1,163) | — |
| Net current period other comprehensive income | 9,202 | 1,210 | 14,506 | 1,738 |
| Ending balance accumulated other comprehensive income | $ 26,986 | $ 968 | $ 26,986 | $ 968 |

(1) Other comprehensive income for the three and six months ended June 30, 2013 includes income tax expense of $6.3 million and $10.0 million, respectively.

(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 2⁵¤₈ percent convertible subordinated notes. Consistent with how we accounted for our 2⁵¤₈ percent notes, we account for our 2¾ percent notes by separating the liability and equity components of the instrument in a manner that reflects our nonconvertible debt borrowing rate. As a result, we assigned a value to the debt component of our 2¾ percent notes equal to the estimated fair value of similar debt instruments without the conversion feature, which resulted in us recording the debt instrument at a discount. We are amortizing the debt discount over the life of these 2¾ percent notes as additional non-cash interest expense utilizing the effective interest method.

**Segment information**

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



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**Stock-based compensation expense**

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

We use the Black-Scholes model to estimate the fair value of stock options granted and stock purchase rights under the ESPP. The expected term of stock options granted represents the period of time that we expect them to be outstanding. We estimate the expected term of options granted based on historical exercise patterns. For the six months ended June 30, 2013 and 2012, we used the following weighted-average assumptions in our Black-Scholes calculations:

*Employee Stock Options:*

| | Six Months Ended June 30, | |
|---|---|---|
| | 2013 | 2012 |
| Risk-free interest rate | 1.0% | 0.8% |
| Dividend yield | 0.0% | 0.0% |
| Volatility | 51.5% | 51.1% |
| Expected life | 5.1 years | 5.1 years |

*ESPP:*

| | Six Months Ended June 30, | |
|---|---|---|
| | 2013 | 2012 |
| Risk-free interest rate | 0.1% | 0.1% |
| Dividend yield | 0.0% | 0.0% |
| Volatility | 61.4% | 42.3% |
| Expected life | 6 months | 6 months |

*Board of Director Stock Options:*

| | Six Months Ended June 30, |
|---|---|
| | 2013 |
| Risk-free interest rate | 2.3% |
| Dividend yield | 0.0% |
| Volatility | 52.4% |
| Expected life | 7.3 years |

For the six months ended June 30, 2012, we did not grant stock options to our Board of Directors.

The fair value of RSUs is based on the market price of our common stock on the date of grant. RSUs vest annually over a four year period. The weighted-average grant date fair value of RSUs granted to employees for the six months ended June 30, 2013 and 2012 was $14.48 and $7.60, respectively.

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

| | Three Months Ended June 30, | | Six Months Ended June 30, | |
|---|---|---|---|---|
| | 2013 | 2012 | 2013 | 2012 |
| Research and development | $ 2,252 | $ 2,073 | $ 4,798 | $ 4,008 |
| General and administrative | 384 | 387 | 707 | 719 |
| Total | $ 2,636 | $ 2,460 | $ 5,505 | $ 4,727 |

As of June 30, 2013, total unrecognized estimated non-cash stock-based compensation expense related to non-vested stock options and RSUs was $9.7 million and $3.3 million, respectively. We will adjust total unrecognized compensation cost for future changes in estimated forfeitures. We expect to recognize the cost of non-cash, stock-based compensation expense related to non-vested stock options and RSUs over a weighted average amortization period of 1.3 years and 1.9 years, respectively.

**Impact of recently issued accounting standards**

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

## 3. Investments

As of June 30, 2013, we have primarily invested our excess cash in debt instruments of the U.S. Treasury, financial institutions, corporations, and U.S. government agencies with strong credit ratings and an investment grade rating at or above A-1, P-1 or F-1 by Moody's, Standard & Poor's (S&P) or Fitch, respectively. We have established guidelines relative to diversification and maturities that maintain safety and liquidity. We periodically review and modify these guidelines to maximize trends in yields and interest rates without compromising safety and liquidity.

The following table summarizes the contract maturity of the available-for-sale securities we held as of June 30, 2013:

| | |
|---|---|
| One year or less | 57% |
| After one year but within two years | 26% |
| After two years but within three years | 17% |
| Total | 100% |

As illustrated above, we primarily invest our excess cash in short-term instruments with 83 percent of our available-for-sale securities having a maturity of less than two years.

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





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

| June 30, 2013 | Amortized Cost | Unrealized Gains | Unrealized Losses | Other-Than-Temporary Impairment Loss | Estimated Fair Value |
|---|---|---|---|---|---|
| Available-for-sale securities: | | | | | |
| Corporate debt securities (1) | $ 134,045 | $ 60 | $ (88) | $ — | $ 134,017 |
| Debt securities issued by U.S. government agencies (1) | 23,887 | — | (85) | — | 23,802 |
| Debt securities issued by the U.S. Treasury | 5,023 | 4 | — | — | 5,027 |
| Debt securities issued by states of the United States and political subdivisions of the states | 11,989 | 35 | — | — | 12,024 |
| Total securities with a maturity of one year or less | 174,944 | 99 | (173) | — | 174,870 |
| Corporate debt securities | 103,219 | 23 | (546) | — | 102,696 |
| Debt securities issued by U.S. government agencies | 10,002 | 25 | (3) | — | 10,024 |
| Debt securities issued by the U.S. Treasury | 8,340 | 14 | — | — | 8,354 |
| Debt securities issued by states of the United States and political subdivisions of the states | 8,771 | 5 | (22) | — | 8,754 |
| Total securities with a maturity of more than one year | 130,332 | 67 | (571) | — | 129,828 |
| Total | $ 305,276 | $ 166 | $ (744) | $ — | $ 304,698 |

| June 30, 2013 | Cost Basis | Unrealized Gains | Unrealized Losses | Other-Than-Temporary Impairment Loss | Estimated Fair Value |
|---|---|---|---|---|---|
| Equity securities: | | | | | |
| Regulus Therapeutics Inc. | $ 15,525 | $ 46,665 | $ — | $ — | $ 62,190 |
| Current portion (included in Other current assets) | 1,538 | 776 | — | (880) | 1,434 |
| Long-term portion (included in Deposits and other | 625 | — | — | — | 625 |

| | | | | | |
|---|---|---|---|---|---|
| assets) | | | | | |
| Total | $ 17,688 | $ 47,441 | $ — | $ (880) | $ 64,249 |



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

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

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

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

| | | Less than 12 months of temporary impairment | |
|---|---|---|---|
| | Number of Investments | Estimated Fair Value | Unrealized Losses |
| Corporate debt securities | 85 | $ 152,051 | $ (634) |
| Debt securities issued by U.S. government agencies | 7 | 25,342 | (88) |
| Debt securities issued by states of the United States and political subdivisions of the states | 6 | 7,823 | (22) |
| Total temporarily impaired securities | 98 | $ 185,216 | $ (744) |

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.



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**4. Fair Value Measurements**

We use a three-tier fair value hierarchy to prioritize the inputs used in our fair value measurements. These tiers include: Level 1, defined as observable inputs such as quoted prices in active markets for identical assets, which includes our money market funds and treasury securities classified as available-for-sale securities and an investment in equity securities in a publicly-held biotechnology company; Level 2, defined as inputs other than quoted prices in active markets that are either directly or indirectly observable, which includes our fixed income securities and commercial paper classified as available-for-sale securities; and Level 3, defined as unobservable inputs in which little or no market data exists, therefore requiring an entity to develop its own assumptions. Our Level 3 investments include investments in the equity securities of publicly-held biotechnology companies for which we calculated a lack of marketability discount because there are restrictions on when we can trade the securities. The majority of our securities have been classified as Level 2. We obtain the fair value of our Level 2 investments from our custodian banks or from a professional pricing service. We validate the fair value of our Level 2 investments by understanding the pricing model used by the custodian bank or professional pricing service provider and comparing that fair value to the fair value based on observable market prices. During the three and six months ended June 30, 2013 and 2012 there were no transfers between our Level 1 and Level 2 investments. We use the end of reporting period method for determining transfers between levels.

We measure the following major security types at fair value on a recurring basis. We break down the inputs used to measure fair value for these assets at June 30, 2013 and December 31, 2012 as follows (in thousands):

| | At June 30, 2013 | Quoted Prices in Active Markets (Level 1) | Significant Other Observable Inputs (Level 2) | Significant Unobservable Inputs (Level 3) |
|---|---|---|---|---|
| Cash equivalents (1) | $ 287,759 | $ 277,272 | $ 10,487 | $ — |
| Corporate debt securities (2) | 231,216 | — | 231,216 | — |
| Debt securities issued by U.S. government agencies (2) | 28,837 | — | 28,837 | — |
| Debt securities issued by the U.S. Treasury (2) | 13,381 | 13,381 | — | — |
| Debt securities issued by states of the United States and political subdivisions of the states (2) | 20,778 | — | 20,778 | — |
| Investment in Regulus Therapeutics Inc. | 62,190 | — | — | 62,190 |
| Equity securities (3) | 1,434 | 1,434 | — | — |
| Total | $ 645,595 | $ 292,087 | $ 291,318 | $ 62,190 |

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

(1) Included in cash and cash equivalents on our condensed consolidated balance sheet.

(2) Included in short-term investments on our condensed consolidated balance sheet.

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



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We classified the fair value measurements of our investments in the equity securities of Regulus and Sarepta Therapeutics, Inc., or Sarepta, as Level 3. We calculated a lack of marketability discount on the fair value of these investments because of trading restrictions on the securities. We consider the inputs we used to calculate the lack of marketability discount Level 3 inputs and, as a result, we categorized these investments as Level 3. We determined the lack of marketability discount by using a Black-Scholes model to value a hypothetical put option to approximate the cost of hedging the stock until the restriction ends. In the first quarter of 2013, we sold all of the common stock of Sarepta that we owned resulting in a realized gain of $1.1 million. As of June 30, 2013, our Level 3 investments consisted of our investment in Regulus, with a gross fair value of $69.2 million less a lack of marketability discount of $7.0 million for a net carrying value of $62.2 million. As of December 31, 2012, our Level 3 investments consisted of our investment in Regulus and Sarepta with a gross fair value of $44.4 million and $1.0 million, respectively, less a lack of marketability discount of $10.8 million and $296,000, respectively, for a net carrying value of $33.6 million and $728,000, respectively.

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

| | Investments Valued Using Level 3 Inputs |
|---|---|
| Balance at December 31, 2012 | $ 34,350 |
| Total gains and losses: | |
| Included in gain on investments | (1,163) |
| Included in accumulated other comprehensive income (loss) | 29,043 |
| Cost basis of shares sold | (40) |
| Balance at June 30, 2013 | $ 62,190 |

**Other Fair Value Disclosures**

Our 2¾ percent convertible notes had a fair value of $357.2 million at June 30, 2013. 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. Long-Term Obligations

**Equipment Financing Arrangement**

In October 2008, we entered into an equipment financing loan agreement and in September 2009 and June 2012, we amended the loan agreement to increase the aggregate maximum amount of principal we could draw under the agreement. Each draw down under the loan agreement has a term of three years, with principal and interest payable monthly. Interest on amounts we borrow under the loan agreement is based upon the three year interest rate swap at

the time we make each draw down plus 3.5 or four percent, depending on the date of the draw. We are using the equipment purchased under the loan agreement as collateral. In June 2012, we drew down $9.1 million in principal under the loan agreement at an interest rate of 4.12 percent and in June 2013 we drew down $2.5 million in principal at an interest rate of 4.38 percent. As of June 30, 2013, our outstanding borrowings under this loan agreement were at a weighted average interest rate of 4.54 percent and we can borrow up to an additional $3.4 million in principal to finance the purchase of equipment until April 2014. The carrying balance under this loan agreement at June 30, 2013 and December 31, 2012 was $9.9 million and $10.0 million, respectively. We will continue to use equipment lease financing as long as the terms remain commercially attractive.

**6. Concentration of Business Risk**

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

| | Three Months Ended June 30, | | Six Months Ended June 30, | |
|---|---|---|---|---|
| | 2013 | 2012 | 2013 | 2012 |
| Partner A | 20% | 90% | 40% | 84% |
| Partner B | 6% | 4% | 15% | 6% |
| Partner C | 40% | 0% | 22% | 0% |
| Partner D | 19% | 4% | 14% | 5% |



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Contract receivables from four significant partners comprised approximately 89 percent of our contract receivables at June 30, 2013. Contract receivables from four significant partners comprised approximately 83 percent of our contract receivables at December 31, 2012.

**7. Income Taxes**

Intraperiod tax allocation rules require us to allocate our provision for income taxes between continuing operations and other categories of earnings, such as other comprehensive income. In periods in which we have a year-to-date pre-tax loss from continuing operations and pre-tax income in other categories of earnings, such as other comprehensive income, we must allocate the tax provision to the other categories of earnings. We then record a related tax benefit in continuing operations. During the first half of 2013, we recorded unrealized gains on our investments in available-for-sale securities in other comprehensive income net of taxes. As a result, we recorded a $1.2 million tax benefit on our condensed consolidated statements of operations and a $9.9 million tax expense in other comprehensive income for the six months ended June 30, 2013.

**8. Collaborative Arrangements and Licensing Agreements**

**Traditional Pharmaceutical Alliances and Licensing**

*AstraZeneca*

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

Together with AstraZeneca, we are evaluating ISIS-STAT3$_{Rx}$ in patients with advanced cancer. AstraZeneca is conducting a Phase 1b/2a clinical study of ISIS-STAT3$_{Rx}$ in patients with advanced metastatic hepatocellular carcinoma, or HCC. We are concurrently completing a clinical study evaluating ISIS-STAT3$_{Rx}$ in patients with advanced lymphomas, including patients with diffuse large b-cell lymphoma. We are responsible for completing our clinical study in patients with advanced lymphomas and AstraZeneca is responsible for all other development activities for ISIS-STAT3$_{Rx}$. We are also advancing ISIS-AR$_{Rx}$, an antisense drug designed to treat patients with prostate cancer by inhibiting the production of the androgen receptor, or AR. In June 2013, we earned a $10 million milestone payment when AstraZeneca added a second development candidate, ISIS-AR$_{Rx}$, to our collaboration. If AstraZeneca successfully develops drugs under all three programs, we could receive substantive milestone payments of more than $970 million, including up to $315.5 million for the achievement of development milestones and up to $655 million for the achievement of regulatory milestones. We could earn the next milestone payment of up to $50 million if we meet pre-agreed efficacy and safety criteria in our ongoing ISIS-STAT3$_{Rx}$ study in patients with advanced cancer.

During the three and six months ended June 30, 2013, we earned revenue of $15.3 million and $17.8 million, respectively, from our relationship with AstraZeneca, which represented 40 percent and 22 percent, respectively, of our total revenue for those periods. Our balance sheets at June 30, 2013 and December 31, 2012 included deferred revenue of $15.4 million and $15.7 million, respectively, related to our relationship with AstraZeneca.

*Biogen Idec*

We have established three strategic collaborations with Biogen Idec that broaden and expand our severe and rare disease franchise. In January 2012, we entered into a global collaboration agreement with Biogen Idec to develop and commercialize ISIS-SMN$_{Rx}$ for the treatment of SMA. Under the terms of the agreement, we received an upfront payment of $29 million and are eligible to receive up to $45 million, of which $3.5 million has been earned, in substantive milestone payments associated with the clinical development of ISIS-SMN$_{Rx}$ prior to licensing. We are responsible for developing 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 April 2013, we initiated a Phase 2 study of ISIS-SMN$_{Rx}$ in infants with SMA, which began the Phase 2/3 program for ISIS-SMN$_{Rx}$. We earned a $3.5 million milestone payment from Biogen Idec in May 2013 when we dosed the first infant in this Phase 2 study. The $3.5 million milestone payment is the first of the four payments under the March 2013 amendment to the payment terms for the $18 million milestone payment we could earn for the progression of this Phase 2/3 study in infants. We will earn a $2.0 million milestone payment, the second of four payments, if we dose the first patient in the second cohort of this

study. We are also eligible to receive up to $150 million in substantive milestone payments if Biogen Idec achieves pre-specified regulatory milestones. In addition, we are eligible to receive up to double-digit royalties on any product sales of ISIS-$SMN_{Rx}$.



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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. Under the terms of the agreement, we received an upfront payment of $12 million and are eligible to receive up to $59 million in substantive milestone payments associated with the development of the DMPK-targeting drug prior to licensing. We are responsible for global development of the drug through the completion of a Phase 2 clinical trial. Biogen Idec has the option to license the drug through the completion of the Phase 2 trial. We are also eligible to receive up to $130 million in substantive milestone payments if Biogen Idec achieves pre-specified regulatory milestones. In addition, we are eligible to receive up to double-digit royalties on any product sales of the drug. We will earn the next milestone payment of $10 million if we initiate an IND-enabling toxicology study for our DMPK program.

In December 2012, we and Biogen Idec entered into a third and separate collaboration to develop and commercialize novel antisense drugs to three targets to treat neurological or neuromuscular diseases. We are responsible for the development of the drugs through the completion of the initial Phase 2 clinical study. Biogen Idec has the option to license a drug from each of the three programs through the completion of Phase 2 studies. Under the terms of the agreement, we received an upfront payment of $30 million and are eligible to receive development milestone payments to support research and development of each program including a $10 million milestone payment per program upon initiation of an IND-enabling toxicology study. We are also eligible to receive up to another $200 million in a license fee and regulatory milestone payments per program including up to $130 million in substantive milestone payments if Biogen Idec achieves pre-specified regulatory milestones. In addition, we are eligible to receive double-digit royalties on any product sales of drugs resulting from each of the three programs. We will earn the next milestone payment of $10 million if we initiate an IND-enabling toxicology study for a development candidate identified under this collaboration.

During the three and six months ended June 30, 2013, we earned revenue of $7.4 million and $11.2 million, respectively, from our relationships with Biogen Idec, which represented 19 percent and 14 percent, respectively, of our total revenue for those periods. In comparison, we earned revenue of $1.8 million and $3.6 million for the same periods in 2012. Our balance sheets at June 30, 2013 and December 31, 2012 included deferred revenue of $55.9 million and $62.6 million, respectively, related to the upfront payments.

*Genzyme Corporation, a Sanofi company*

In January 2008, we entered into a strategic alliance with Genzyme focused on the licensing and co-development of KYNAMRO. The license and co-development agreement provides Genzyme with exclusive worldwide rights for all therapeutic purposes to our patents and know-how related to KYNAMRO, including the key product related patents and their foreign equivalents pending or granted in various countries outside the United States, including in the European Union via the European Patent Convention, Japan, Canada, Australia, South Africa and India. In addition, we agreed that we would not develop or commercialize another oligonucleotide-based compound designed to modulate apo-B by binding to the messenger RNA, or mRNA, encoding apo-B, throughout the world.

The transaction included a $175 million licensing fee, a $150 million equity investment in our stock in which we issued Genzyme five million shares of our common stock, and a share of worldwide profits on KYNAMRO and follow-on drugs ranging from 30 percent to 50 percent of all commercial sales. In January 2013 we earned a $25 million milestone payment when the FDA approved the NDA for KYNAMRO. We may also receive over $1.5 billion in substantive milestone payments if Genzyme achieves pre-specified events, including up to $700 million for the achievement of regulatory milestones and up to $825 million for the achievement of commercialization milestones. The next milestone payment we could earn under our agreement with Genzyme is $25 million upon the earlier of an NDA approval for the use of KYNAMRO to treat patients who have heterozygous FH or annual net revenue equal to or greater than $250 million in a calendar year.

Under this alliance, Genzyme is responsible for the continued development and commercialization of KYNAMRO. We agreed to supply the drug substance for KYNAMRO for the Phase 3 clinical trials and initial commercial launch. Genzyme is responsible for manufacturing the finished drug product for KYNAMRO, including the initial commercial launch supply, and Genzyme will be responsible for the long term supply of KYNAMRO drug substance and finished drug product. As part of the agreement, we contributed the first $125 million in funding for the development costs of KYNAMRO. In 2011, we satisfied our development funding obligation. As such, we and Genzyme shared development expenses equally in 2012 and the first half of 2013. Our shared funding of development expenses will end when KYNAMRO is profitable.



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The license and co-development agreement for KYNAMRO will continue in perpetuity unless we or Genzyme terminate it earlier under the following situations:

- Genzyme may terminate the license and co-development agreement at any time by providing written notice to Isis;
- We may terminate the license and co-development agreement on a country-by-country basis or in its entirety upon Genzyme's uncured failure to use commercially reasonable efforts to develop and commercialize KYNAMRO in the United States, France, Germany, Italy, Spain, the United Kingdom, Japan and Canada; and
- Either we or Genzyme may terminate the license and co-development agreement upon the other party's uncured failure to perform a material obligation under the agreement.

Upon termination of the license and co-development agreement, the license we granted to Genzyme for KYNAMRO will terminate and Genzyme will stop selling the product. In addition, if Genzyme voluntarily terminates the agreement or we terminate the agreement in a country or countries for Genzyme's failure to develop and commercialize KYNAMRO, then the rights to KYNAMRO will revert back to us and we may develop and commercialize KYNAMRO in the countries that are the subject of the termination, subject to a royalty payable to Genzyme.

If we are the subject of an acquisition, then within 180 days following the acquisition, Genzyme may elect to purchase all of our rights to receive payments under the KYNAMRO license and co-development agreement for a purchase price to be mutually agreed to by us and Genzyme, or, if we cannot agree, a fair market value price determined by an independent investment banking firm.

Genzyme has agreed to monthly limits on the number of shares it can sell of the Company's stock that it purchased in February 2008. In addition, Genzyme has agreed that until the earlier of the 10 year anniversary of the KYNAMRO license and co-development agreement or the date Genzyme holds less than two percent of our issued and outstanding common stock, Genzyme will not acquire any additional shares of our common stock without our consent.

The price Genzyme paid for our common stock represented a significant premium over the then fair value of our common stock. In May 2012, we finished amortizing this $100 million premium along with the $175 million licensing fee that we received in the second quarter of 2008. During the three and six months ended June 30, 2013, we earned revenue of $7.5 million and $32.5 million, respectively, from our relationship with Genzyme, which represented 20 percent and 40 percent, respectively, of our total revenue for those periods. In comparison, we earned revenue of $42.8 million and $59.1 million for the same periods in 2012. Our balance sheet at December 31, 2012 included deferred revenue of $3.8 million for KYNAMRO drug substance that we shipped to Genzyme in 2013.

*GlaxoSmithKline*

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

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

Our strategic alliance currently includes five active programs including the ISIS-$TTR_{Rx}$ program. We are eligible to receive on average up to $20 million in milestone payments per program up to Phase 2 proof-of-concept. GSK has the option to license drugs from these programs at Phase 2 proof-of-concept, and if GSK exercises its option to a program it will be responsible for all further development and commercialization of the program. Under the terms of the amended agreement, if GSK successfully develops all five programs for one or more indications and achieves pre-agreed sales targets, we could receive license fees and substantive milestone payments of nearly $1.2 billion, including up to $202.5 million for the achievement of development milestones, up to $526.5 million for the achievement of regulatory milestones and up to $445 million for the achievement of commercialization milestones. We will earn the next $2 milestone payment if we further progress the Phase 2/3 clinical study for ISIS-$TTR_{Rx}$. In addition, we are eligible to receive up to double-digit royalties on sales from any product that GSK successfully commercializes under this alliance.



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During the three and six months ended June 30, 2013, we earned revenue of $2.3 million and $12.2 million, respectively, from our relationship with GSK, which represented six percent and 15 percent, respectively, of our total revenue for those periods. In comparison, we earned revenue of $2.0 million and $4.0 million for the same periods in 2012. Our balance sheets at June 30, 2013 and December 31, 2012 included deferred revenue of $15.4 million and $19.9 million, respectively, related to our relationship with GSK.

*Roche*

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

During the three and six months ended June 30, 2013, we earned revenue of $1.3 million from our relationship with Roche. Our balance sheet at June 30, 2013 included deferred revenue of $28.8 million related to the upfront payment.

**Satellite Company Collaborations**

*Xenon Pharmaceuticals Inc.*

In November 2010, we established a collaboration with Xenon to discover and develop antisense drugs as novel treatments for anemia of chronic disorders, or ACD. We received an upfront payment in the form of a convertible promissory note from Xenon to discover and develop antisense drugs to the targets hemojuvelin and hepcidin. Because repayment of the promissory note was uncertain, we did not record any revenue from the upfront payment when we entered into the agreement. In May 2012, Xenon selected XEN701, a drug designed to inhibit the production of hepcidin, as a development candidate. In June 2013, we earned a $2 million license fee when Xenon exercised its option to an exclusive worldwide license to XEN701. In addition, in June 2013 Xenon repaid the $1.5 million convertible promissory note. We recognized the $2 million license fee and the $1.5 million upfront payment as revenue in the

second quarter of 2013. Under our collaboration agreement with Xenon, we may receive up to $296 million in substantive milestone payments for the achievement of pre-specified milestone events that are met by two independent products, including up to $26 million for the achievement of development milestones, up to $150 million for the achievement of regulatory milestones and up to $120 million for the achievement of commercialization milestones. In addition, we are eligible to receive royalties on future product sales of XEN701 and a portion of sublicense revenue. We will earn the next milestone payment of $3 million if Xenon initiates a Phase 2 clinical trial for XEN701.

During the three and six months ended June 30, 2013, we earned revenue of $3.5 million from our relationship with Xenon.

**External Project Funding**

*CHDI Foundation, Inc.*

Starting in November 2007, CHDI provided financial and scientific support to our HD drug discovery program through our development collaboration. In April 2013, we formed an alliance with Roche to develop treatments for HD. Under the terms of our agreement with CHDI, we will reimburse CHDI for a portion of its support of our HD program out of the payments we receive from Roche. In April 2013, we paid CHDI $1.5 million associated with the signing of the Roche agreement, which we recorded as research and development expense. We will also pay CHDI $1.5 million when we select an HD development candidate. If we achieve certain milestones under our collaboration with Roche, we will make additional payments to CHDI. During the three and six months ended June 30, 2013, we earned revenue of $122,000 and $414,000, respectively, from our relationship with CHDI.



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

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

**Forward-Looking Statements**

In addition to historical information contained in this Report on Form 10-Q, this Report includes forward-looking statements regarding our business, the therapeutic and commercial potential of our technologies and products in development, and the financial position of Isis Pharmaceuticals, Inc. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs, including the commercial potential of KYNAMRO, is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning our programs are described in additional detail in our Annual Report on Form 10-K for the year ended December 31, 2012, which is on file with the U.S. Securities and Exchange Commission, and those identified within this Item in the section entitled "Risk Factors" beginning on page 33 of this Report.

**Overview**

We are the leading company in antisense drug discovery and development, exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs. Antisense technology provides a direct route from genomics to drugs. Our strategy is to do what we do best—to discover and develop unique antisense drugs. The efficiency and broad applicability of our drug discovery platform allows us to discover and develop antisense drugs to treat a wide range of diseases, including cardiovascular, severe and rare, neurologic and metabolic diseases and cancer.

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

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

Our pipeline goes well beyond KYNAMRO. We have a pipeline of 28 drugs in development that represents the potential for significant commercial opportunities in many therapeutic areas. We believe that several of the drugs in our pipeline could reach the market by 2017. For instance, we designed our transthyretin, or TTR, amyloidosis and spinal muscular atrophy, or SMA, drugs to treat patients with severe and rare diseases who have very limited therapeutic options. Because of the significant unmet medical need and the severity of these diseases, new therapeutic approaches could warrant an accelerated path to market. In addition, several of the drugs in our pipeline are advancing through Phase 2 clinical programs and could represent significant near and mid-term licensing opportunities. These drugs, including ISIS-$CRP_{Rx}$ and ISIS-$FXI_{Rx}$, represent substantial commercial opportunities with the potential for Phase 2 data within the next 12 to 18 months. Further, we recently reported encouraging Phase 2 data for ISIS-$APOCIII_{Rx}$ and we plan to advance ISIS-$APOCIII_{Rx}$ into a Phase 3 program early next year. We plan to use the proceeds from our recent public offering of common stock to develop select drugs in our pipeline, such as ISIS-$APOCIII_{Rx}$, to later stages of development prior to partnering.

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

The broad applicability of our drug discovery technology and the clinical successes of the drugs in our pipeline continue to create new partnering opportunities. Since January 2012, we have initiated five new partnerships that involve neurological diseases or cancer, including a strategic alliance with Roche to discover and develop antisense drugs to treat Huntington's disease, three strategic alliances with Biogen Idec to discover and develop antisense drugs for the treatment of neurologic diseases, and a strategic alliance with AstraZeneca to discover and develop antisense drugs to treat cancer. We have received more than $130 million in upfront payments and have the potential to earn more than $2.7 billion in future milestone payments and licensing fees from these partnerships. Since 2007, our partnerships have generated an aggregate of more than $1 billion in payments from upfront and licensing fees, equity purchase payments, milestone payments and research and development funding. In addition, for our current partnered programs we have the potential to earn up to $5.1 billion in future milestone payments. We also have the potential to share in the future commercial success of our inventions and drugs resulting from these partnerships through earn out, profit sharing, or royalty arrangements.

We also work with a consortium of smaller companies that can exploit our drugs and technologies. We call these smaller companies our satellite companies. In this way, we benefit from the disease-specific expertise of our satellite company partners, who are advancing drugs in our pipeline in areas that are outside of our core focus. In addition, we can maintain our broad RNA technology leadership through collaborations with companies such as Alnylam Pharmaceuticals, Inc., or Alnylam, and Regulus Therapeutics Inc., or Regulus, a company we co-founded with Alnylam focused on microRNA therapeutics. In October 2012, Regulus completed an initial public offering. As of June 30, 2013, the carrying value of our investment in Regulus was $62.2 million, demonstrating the value of our satellite company strategy. All of these different types of relationships are part of our unique business model and create near and long-term shareholder value.

We protect our proprietary technologies and products through our substantial patent estate. As an innovator in RNA-targeting drug discovery and development, we design and execute our patent strategy to provide us with extensive protection for our drugs and our technology. With our ongoing research and development, we continue to add to our substantial patent estate. Our patents not only protect our key assets—our technology and our drugs—they also form the basis for lucrative licensing and partnering arrangements. To date, we have generated over $400 million from our intellectual property sale and licensing program that helps support our internal drug discovery and development programs.

**Recent Events**

***Drug Development Highlights***

- We and our partners advanced antisense drugs in our pipeline and reported positive clinical data from three programs.
  - We advanced the Phase 2/3 study of ISIS-TTR$_{Rx}$, a drug to treat patients with familial amyloid polyneuropathy. As a result, we earned $2 million from GlaxoSmithKline.
  - We reported Phase 2 data on ISIS-APOCIII$_{Rx}$ in patients with high to severely high triglycerides on stable fibrates. In this study, ISIS-APOCIII$_{Rx}$ treatment resulted in statistically significant reductions in triglycerides and apoC-III and a statistically significant increase in high-density lipoprotein, or HDL.
  - We reported Phase 2 data on ISIS-APOCIII$_{Rx}$ in patients with high triglycerides and type 2 diabetes at the American Diabetes Association Scientific Sessions. In this study, ISIS-APOCIII$_{Rx}$ treatment resulted in statistically significant reductions in triglycerides and apoC-III and a statistically significant increase in HDL. In this study treated patients also experienced improvements in glucose control and trends toward enhanced insulin sensitivity.
  - We reported Phase 2 data on ISIS-CRP$_{Rx}$ in patients with rheumatoid arthritis, or RA. In this study, patients treated with ISIS-CRP$_{Rx}$ achieved rapid, dose-dependent mean reductions of up to 67 percent in C-reactive protein, or CRP, but failed to demonstrate improvements in signs and symptoms of RA that were sufficiently better than those achieved by patients in the placebo group to justify further development of ISIS-CRP$_{Rx}$ for RA.





  - Dr. David Hong reported Phase 1 data on ISIS-STAT3$_{Rx}$ at the American Society of Clinical Oncology. In this study, treatment with ISIS-STAT3$_{Rx}$ resulted in partial responses that were durable and prolonged in two out of three patients with diffuse large B-cell lymphoma who were refractory to prior chemotherapy treatments.
- We and our partners initiated clinical studies on three drugs in our pipeline.
  - We initiated a Phase 2 study of ISIS-SMN$_{Rx}$ in infants with SMA and earned a $3.5 million milestone payment from Biogen Idec.
  - AstraZeneca initiated a Phase 1b/2a study of ISIS-STAT3$_{Rx}$ in patients with advanced metastatic hepatocellular carcinoma.
  - We initiated a Phase 1 study of ISIS-APOA$_{Rx}$, an antisense drug designed to reduce levels of Lp(a), an atherogenic lipoprotein.
- We and our partners continued to advance our preclinical stage pipeline by adding three drugs into development.
  - AstraZeneca selected ISIS-AR$_{Rx}$ as the second development candidate to advance into development under its collaboration with us. As a result, we earned a $10 million milestone payment from AstraZeneca.
  - Xenon selected XEN701 as a development candidate and licensed XEN701 from us. As a result we earned $3.5 million from Xenon.
  - We added a new drug to our pipeline, ISIS-ANGTL3$_{Rx}$, for the treatment of hyperlipidemia.

***Corporate Highlights***

- We successfully completed a public offering of common stock raising $173.2 million in net proceeds. We plan to use the proceeds from this offering to pursue Phase 3 development of ISIS-APOCIII$_{Rx}$, retain additional drugs longer in development and advance the rest of our pipeline.
- We added Breaux Castleman, a senior executive with extensive business experience, to our Board of Directors.
- We received $6 million from AstraZeneca related to the continuation of the research collaboration between us and AstraZeneca to discover and develop novel antisense drugs to treat cancer.
- We formed a new alliance with Roche to discover and develop antisense drugs to treat Huntington's disease.
    - We received a $30 million upfront payment and are eligible to receive up to $362 million in a license fee, pre-licensing and post-licensing milestone payments, including up to $80 million in commercial milestones.
    - In addition, we are eligible to receive up to $136.5 million in milestone payments for each additional drug successfully developed plus 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 on sales of drugs arising from the alliance.

**Critical Accounting Policies**

We prepare our condensed consolidated financial statements in conformity with accounting principles generally accepted in the United States of America. As such, we make certain estimates, judgments and assumptions that we believe are reasonable, based upon the information available to us. These judgments involve making estimates about the effect of matters that are inherently uncertain and may significantly impact our quarterly or annual results of operations and financial condition. Each quarter, our senior management discusses the development, selection and disclosure of such estimates with our audit committee of our board of directors. There are specific risks associated with these critical accounting policies and we caution that future events rarely develop exactly as one may expect, and that best estimates may require adjustment. A discussion of these specific risks can be found in Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations", included in our Annual Report on Form 10-K for the year ended December 31, 2012. There have been no material changes to our critical accounting policies and estimates from the information provided in that discussion.

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

- Assessing the propriety of revenue recognition and associated deferred revenue;
- Determining the proper valuation of investments in marketable securities and other equity investments;
- Assessing the recoverability of long-lived assets, including property and equipment, intellectual property and licensed technology;
- Determining the proper valuation of inventory;



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- Determining the appropriate cost estimates for unbilled preclinical studies and clinical development activities;
- Estimating our net deferred income tax asset valuation allowance;
- Determining the fair value of convertible debt without the conversion feature;
- Determining when we are the primary beneficiary for entities that we identify as variable interest entities; and
- Determining the fair value of stock-based compensation, including the expected life of the option, the expected stock price volatility over the term of the expected life and estimated forfeitures.

**Results of Operations**

**Revenue**

Total revenue for the three and six months ended June 30, 2013 was $38.1 million and $81.5 million, respectively, compared to $47.3 million and $70.6 million for the same periods in 2012. Our revenue fluctuates based on the nature and timing of payments under agreements with our partners, including license fees, milestone-related payments and other payments. For example, we earned $49.5 million in milestone and licensing payments in the first half of 2013 comprised of:

- $25 million from Genzyme when the FDA approved the KYNAMRO NDA;
- $10 million when AstraZeneca added a second development candidate, ISIS-AR$_{Rx}$, to our collaboration;
- $7.5 million from GSK when we initiated the Phase 2/3 study of ISIS-TTR$_{Rx}$;
- $3.5 million from Biogen Idec when we dosed the first infant in a Phase 2 study of ISIS-SMN$_{Rx}$; and
- $3.5 million when Xenon licensed a development candidate, XEN701, from us.

In comparison, we earned a $25 million milestone payment in the first half of 2012 from Genzyme when the FDA accepted the NDA for KYNAMRO. Our revenue in the first half of 2013 also included more than $13 million in new revenue we earned from our alliances with AstraZeneca, Biogen Idec and Roche. These increases were offset, in part, by the completion of the amortization of the upfront payments associated with our Genzyme collaboration.

*Research and Development Revenue Under Collaborative Agreements*

Research and development revenue under collaborative agreements for the three and six months ended June 30, 2013 was $37.6 million and $79.5 million, respectively, compared to $47.1 million and $69.0 million for the same periods in 2012. The increase in the first half of 2013 was primarily due to an increase in milestone payments compared to the same period in 2012 and new revenue from our alliances with AstraZeneca, Biogen Idec and Roche. These increases were offset, in part, by the completion of the amortization of the upfront payments associated with our Genzyme collaboration.

*Licensing and Royalty Revenue*

Our revenue from licensing activities and royalties for the three and six months ended June 30, 2013 was $477,000 and $1.9 million, respectively, and was essentially flat when compared to $200,000 and $1.6 million for the same periods in 2012.

**Operating Expenses**

Operating expenses of $46.0 million and $87.8 million, respectively, for the three and six months ended June 30, 2013 were nearly flat compared to $43.6 million and $85.3 million for the same periods in 2012.

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.



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***Research and Development Expenses***

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

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

| | Three Months Ended June 30, | | Six Months Ended June 30, | |
|---|---|---|---|---|
| | 2013 | 2012 | 2013 | 2012 |
| Research and development expenses | $ 40,379 | $ 38,362 | $ 76,146 | $ 75,141 |
| Non-cash compensation expense related to equity awards | 2,252 | 2,073 | 4,798 | 4,008 |
| Total research and development | $ 42,631 | $ 40,435 | $ 80,944 | $ 79,149 |

For the three and six months ended June 30, 2013, our total research and development expenses were $40.4 million and $76.1 million, respectively, and were nearly flat compared to $38.4 million and $75.1 million for the same periods in 2012. All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Discovery

We use our proprietary antisense technology to generate information about the function of genes and to determine the value of genes as drug discovery targets. We use this information to direct our own antisense drug discovery research, and that of our antisense drug discovery partners. Antisense drug discovery is also the function within Isis that is responsible for advancing antisense core technology.

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

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

| | Three Months Ended June 30, | | Six Months Ended June 30, | |
|---|---|---|---|---|
| | 2013 | 2012 | 2013 | 2012 |
| Antisense drug discovery expenses | $ 10,854 | $ 8,429 | $ 20,251 | $ 16,793 |
| Non-cash compensation expense related to equity awards | 682 | 600 | 1,451 | 1,165 |
| Total antisense drug discovery | $ 11,536 | $ 9,029 | $ 21,702 | $ 17,958 |

Antisense drug discovery costs for the three and six months ended June 30, 2013 were $10.9 million and $20.3 million, respectively, compared to $8.4 million and $16.8 million for the same periods in 2012. Expenses increased in 2013 compared to 2012 primarily due to a $1.5 million payment we made to CHDI in the second quarter of 2013. Under the terms of our agreement with CHDI, we reimbursed CHDI for a portion of its support of our HD program out of the $30 million upfront payment we received from our recent alliance with Roche to develop treatments for HD. All amounts exclude non-cash compensation expense related to equity awards.



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Antisense Drug Development

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

| | Three Months Ended June 30, | | Six Months Ended June 30, | |
|---|---|---|---|---|
| | 2013 | 2012 | 2013 | 2012 |
| KYNAMRO | $ 1,647 | $ 2,431 | $ 3,591 | $ 5,466 |
| ISIS-TTR$_{Rx}$ | 1,218 | 1,275 | 1,984 | 2,544 |
| Other antisense development products | 13,710 | 13,221 | 23,588 | 24,149 |
| Development overhead costs | 1,743 | 1,549 | 3,561 | 3,450 |
| Non-cash compensation expense related to equity awards | 721 | 724 | 1,576 | 1,381 |
| Total antisense drug development | $ 19,039 | $ 19,200 | $ 34,300 | $ 36,990 |

Antisense drug development expenses were $18.3 million and $32.7 million, respectively, for the three and six months ended June 30, 2013, compared to $18.5 million and $35.6 million for the same periods in 2012. Expenses decreased in the first half of 2013 compared to the same period in 2012 primarily due to a decrease in expenses related to KYNAMRO. Expenses for ISIS-TTR$_{Rx}$ also decreased slightly compared to the same period in 2012. We initiated a Phase 2/3 clinical study for ISIS-TTR$_{Rx}$ in February 2013, for which we incurred a significant portion of the start-up expenses in 2012. We expect expenses for this study to increase as the study progresses throughout the year. All amounts exclude non-cash compensation expense related to equity awards.

We may conduct multiple clinical trials on a drug candidate, including multiple clinical trials for the various indications we may be studying. Furthermore, as we obtain results from trials we may elect to discontinue clinical trials for certain drug candidates in certain indications in order to focus our resources on more promising drug candidates or indications. Our Phase 1 and Phase 2 programs are clinical research programs that fuel our Phase 3 pipeline. When our products are in Phase 1 or Phase 2 clinical trials, they are in a dynamic state in which we continually adjust the development strategy for each product. Although we may characterize a product as “in Phase 1” or “in Phase 2,” it does not mean that we are conducting a single, well-defined study with dedicated resources. Instead, we allocate our internal resources on a shared basis across numerous products based on each product’s particular needs at that time. This means we are constantly shifting resources among products. Therefore, what we spend on each product during a particular period is usually a function of what is required to keep the products progressing in clinical development, not what products we think are most important. For example, the number of people required to start a new study is large, the number of people required to keep a study going is modest and the number of people required to finish a study is large. However, such fluctuations are not indicative of a shift in our emphasis from one product to another and cannot be used to accurately predict future costs for each product. And, because we always have numerous products in preclinical and early stage clinical research, the fluctuations in expenses from product to product, in large part, offset one another. If we partner a drug, it may affect the size of a trial, its timing, its total cost and the timing of the related cost. We have partnered 15 of our 28 drug candidates, which substantially reduces our development 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 June 30, | | Six Months Ended June 30, | |
|---|---|---|---|---|
| | 2013 | 2012 | 2013 | 2012 |
| Manufacturing and operations | $ 4,354 | $ 5,115 | $ 8,575 | $ 9,685 |
| Non-cash compensation expense related to equity awards | 305 | 302 | 659 | 564 |
| Total manufacturing and operations | $ 4,659 | $ 5,417 | $ 9,234 | $ 10,249 |



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Manufacturing and operations expenses were $4.4 million and $8.6 million, respectively, for the three and six months ended June 30, 2013 compared to $5.1 million and $9.7 million for the same periods in 2012. Expenses decreased in the first half of 2013 compared to the same period in 2012 primarily because we manufactured less KYNAMRO drug substance. We were responsible for manufacturing the drug substance that was necessary for the initial launch of KYNAMRO and Genzyme is responsible for the long-term supply of KYNAMRO drug substance. Because we are transitioning manufacturing responsibility to Genzyme, our KYNAMRO manufacturing costs have decreased. All amounts exclude non-cash compensation expense related to equity awards.

R&D Support

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

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

| | Three Months Ended June 30, | | Six Months Ended June 30, | |
|---|---|---|---|---|
| | 2013 | 2012 | 2013 | 2012 |
| Personnel costs | $ 2,318 | $ 2,274 | $ 4,656 | 4,541 |
| Occupancy | 1,688 | 1,675 | 3,334 | 3,403 |
| Depreciation and amortization | 1,076 | 1,321 | 2,156 | 2,460 |
| Insurance | 280 | 271 | 567 | 581 |
| Other | 1,491 | 801 | 3,883 | 2,069 |

| | | | | |
|---|---|---|---|---|
| Non-cash compensation expense related to equity awards | 544 | 447 | 1,112 | 898 |
| Total R&D support | $ 7,397 | $ 6,789 | $ 15,708 | $ 13,952 |

R&D support costs for the three and six months ended June 30, 2013 were $6.9 million and $14.6 million, respectively, compared to $6.3 million and $13.1 million for the same periods in 2012. Expenses increased in the first half of 2013 compared to the same period in 2012 primarily due to litigation costs for our patent infringement lawsuit against Santaris Pharma A/S. All amounts exclude non-cash compensation expense related to equity awards.

***General and Administrative Expenses***

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

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

| | Three Months Ended June 30, | | Six Months Ended June 30, | |
|---|---|---|---|---|
| | 2013 | 2012 | 2013 | 2012 |
| General and administrative expenses | $ 3,005 | $ 2,822 | $ 6,104 | $ 5,466 |
| Non-cash compensation expense related to equity awards | 384 | 387 | 707 | 719 |
| Total general and administrative | $ 3,389 | $ 3,209 | $ 6,811 | $ 6,185 |

General and administrative expenses were $3.0 million and $6.1 million, respectively, for the three and six months ended June 30, 2013, and increased slightly compared to $2.8 million and $5.5 million for the same periods in 2012 primarily due to higher personnel expenses. All amounts exclude non-cash compensation expense related to equity awards.

***Equity in Net Loss of Regulus Therapeutics Inc.***

We did not recognize any equity in net loss of Regulus for the three and six months ended June 30, 2013, compared to equity in net loss of Regulus of $163,000 and $1.1 million for the same periods in 2012. We used the equity method of accounting to account for our investment in Regulus until Regulus' IPO in October 2012. In the fourth quarter of 2012, we began accounting for our investment at fair value because we now own less than 20 percent of Regulus' common stock and we no longer have significant influence over the operating and financial policies of Regulus.



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***Investment Income***

Investment income for the three and six months ended June 30, 2013 was $589,000 and $967,000, respectively, compared to $477,000 and $1.1 million for the same periods in 2012. The decrease in investment income in 2013 is primarily due to a lower average return on our investments resulting from current market conditions. We expect investment income to increase in the second half of 2013 as a result of the additional cash we received from our equity offering in the second quarter.

***Interest Expense***

Interest expense for the three and six months ended June 30, 2013 was $4.8 million and $9.6 million, respectively, compared to $5.2 million and $10.4 million for the same periods in 2012. The decrease in interest expense is primarily because the debt discount we are amortizing as additional non-cash interest expense for the $2^{3}/_{4}$ percent convertible senior notes is less than the amount we were amortizing for the $2^{5}/_{8}$ percent convertible subordinated notes we redeemed in September 2012.

***Gain on Investments, net***

Gain on investments for the three and six months ended June 30, 2013 was $840,000 and $1.9 million, respectively, compared to $2,000 and $19,000 for the same periods in 2012. The gain on investments in the first half of 2013 was primarily due to $1.1 million we received in the first quarter of 2013 when we sold the stock we held in Sarepta Therapeutics, Inc. and the $844,000 payment we received from Pfizer, Inc. in the second quarter of 2013 related to its acquisition of Excaliard Pharmaceuticals, Inc. These gains demonstrate the value that we are realizing from our satellite company strategy.

***Income Tax Benefit (Expense)***

We recognized a tax benefit of $1.2 million for both the three and six months ended June 30, 2013, compared to tax expense of $2,000 for the six months ended June 30, 2012. The tax benefit we recorded in 2013 is primarily related to the unrealized gain associated with our investment in Regulus. This unrealized gain reflects the increase in Regulus' stock price during the first half of 2013.

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

Net loss for the three and six months ended June 30, 2013 was $10.1 million and $11.8 million, respectively, compared to $1.2 million and $25.2 million for the same periods in 2012. Basic and diluted net loss per share for the three and six months ended June 30, 2013 was $0.09 per share and $0.11 per share, respectively, compared to $0.01 per share and $0.25 per share for the same periods in 2012. Our net loss for the first half of 2013 was significantly lower than in 2012 primarily due to the revenue we earned from our partners in the first half of 2013.

**Liquidity and Capital Resources**

We have financed our operations with revenue primarily from research and development collaborative agreements. Additionally, we have earned revenue from the sale or licensing of our intellectual property. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From our inception through June 30, 2013 we have earned approximately $1.2 billion in revenue from contract research and development and the sale and licensing of our intellectual property. From the time we were founded through June 30, 2013, we have raised net proceeds of approximately $1.1 billion from the sale of our equity securities and we have borrowed approximately $786.9 million under long-term debt arrangements to finance a portion of our operations.

As of June 30, 2013, we had cash, cash equivalents and short-term investments of $590.8 million and stockholders' equity of $401.1 million. In comparison, we had cash, cash equivalents and short-term investments of $374.4 million and stockholders' equity of $182.8 million at December 31, 2012. We received a substantial amount of cash in the first six months of 2013, including:

- $173.2 million in net proceeds from a public offering of our common stock;
- $93.0 million in payments from our partners; and
- $36.9 million in proceeds from stock option exercises.

At June 30, 2013, we had consolidated working capital of $582.1 million, compared to $349.1 million at December 31, 2012. Our working capital increased in 2013 primarily due to the increase in cash and the increase in the value of our ownership in Regulus. At June 30, 2013, the carrying value of our investment in Regulus increased to $62.2 million compared to $33.6 million at December 31, 2012.



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As of June 30, 2013, our debt and other obligations totaled $284.4 million, and were essentially flat, compared to $284.1 million at December 31, 2012. In June 2013, we drew down $2.5 million on our equipment financing arrangement and this increase was partially offset by rent and principal payments we made in the first half of 2013 on our lease obligations and notes payable.

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

| | Payments Due by Period (in millions) | | | | |
|---|---|---|---|---|---|
| **Contractual Obligations (selected balances described below)** | **Total** | **Less than 1 year** | **1-3 years** | **3-5 years** | **After 5 years** |
| 2¾ percent Convertible Senior Notes (principal and interest payable) | $ 237.3 | $ 5.5 | $ 11.1 | $ 11.1 | $ 209.6 |
| Facility Rent Payments | $ 140.8 | $ 6.0 | $ 12.5 | $ 13.3 | $ 109.0 |
| Equipment Financing Arrangements (principal and interest payable) | $ 10.4 | $ 5.0 | $ 5.3 | $ 0.1 | $ — |
| Other Obligations (principal and interest payable) | $ 1.4 | $ 0.1 | $ 0.1 | $ 0.1 | $ 1.1 |
| Capital Lease | $ 0.4 | $ 0.2 | $ 0.2 | $ — | $ — |
| Operating Leases | $ 27.3 | $ 1.5 | $ 3.0 | $ 3.0 | $ 19.8 |
| Total | $ 417.6 | $ 18.3 | $ 32.2 | $ 27.6 | $ 339.5 |

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

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

In October 2008, we entered into an equipment financing loan agreement and in September 2009 and June 2012, we amended the loan agreement to increase the aggregate maximum amount of principal we could draw under the agreement. Each draw down under the loan agreement has a term of three years, with principal and interest payable monthly. Interest on amounts we borrow under the loan agreement is based upon the three year interest rate swap at the time we make each draw down plus 3.5 or four percent, depending on the date of the draw. We are using the equipment purchased under the loan agreement as collateral. In June 2012, we drew down $9.1 million in principal under the loan agreement at an interest rate of 4.12 percent and in June 2013 we drew down $2.5 million in principal at an interest rate of 4.38 percent. As of June 30, 2013, our outstanding borrowings under this loan agreement were at a weighted average interest rate of 4.54 percent and we can borrow up to an additional $3.4 million in principal to finance the purchase of equipment until April 2014. The carrying balance under this loan agreement at June 30, 2013 and December 31, 2012 was $9.9 million and $10.0 million, respectively. We will continue to use equipment lease financing as long as the terms remain commercially attractive.

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

In addition to contractual obligations, we had outstanding purchase orders as of June 30, 2013 for the purchase of services, capital equipment and materials as part of our normal course of business.

We plan to continue to enter into collaborations with partners to provide for additional revenue to us and we may incur additional cash expenditures related to our obligations under any of the new agreements we may enter into. We currently intend to use our cash, cash equivalents and short-term investments to finance our activities. However, we may also pursue other financing alternatives, like issuing additional shares of our common stock, issuing debt instruments, refinancing our existing debt, or securing lines of credit. Whether we use our existing capital resources or choose to obtain financing will depend on various factors, including the future success of our business, the prevailing interest rate environment and the condition of financial markets generally.

## RISK FACTORS

*Investing in our securities involves a high degree of risk. You should consider carefully the following information about the risks described below, together with the other information contained in this report and in our other public filings in evaluating our business. If any of the following risks actually occur, our business could be materially harmed, and our financial condition and results of operations could be materially and adversely affected. As a result, the trading price of our securities could decline, and you might lose all or part of your investment. We have marked with an asterisk those risk factors that reflect substantive changes from the risk factors included in our Annual Report on Form 10-K for the year ended December 31, 2012.*

### Risks Associated with our Drug Discovery and Development Business

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

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

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

Additionally, in many of the markets where we may sell our drugs in the future, if we cannot agree with the government regarding the price we can charge for our drugs, then we may not be able to sell our drugs in that market.

The degree of market acceptance for KYNAMRO, and any of our other drugs, depends upon a number of factors, including the:

- receipt and scope of regulatory approvals;
- establishment and demonstration in the medical and patient community of the efficacy and safety of our drugs and their potential advantages over competing products;
- cost and effectiveness of our drugs compared to other available therapies;
- patient convenience of the dosing regimen for our drugs; and
- reimbursement policies of government and third-party payors.



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Based on the profile of our drugs, physicians, patients, patient advocates, payors or the medical community in general may not accept and/or use any drugs that we may develop. In addition, cost control initiatives by governments or third party payors could decrease the price received for KYNAMRO or our other drugs or increase patient coinsurance to a level that makes KYNAMRO or our other drugs unaffordable.

**If our drug discovery and development business fails to compete effectively, our drugs will not contribute significant revenues.***

Our competitors engage in all areas of drug discovery throughout the world, are numerous, and include, among others, major pharmaceutical companies and specialized biopharmaceutical firms. Other companies engage in developing antisense technology. Our competitors may succeed in developing drugs that are:

- priced lower than our drugs;
- safer than our drugs;

- more effective than our drugs; or
- more convenient to use than our drugs.

These competitive developments could make our drugs, including KYNAMRO, obsolete or non-competitive.

Certain of our partners are pursuing other technologies or developing other drugs either on their own or in collaboration with others, including our competitors, to treat the same diseases our own collaborative programs target. Competition may negatively impact a partner's focus on and commitment to our drugs and, as a result, could delay or otherwise negatively affect the commercialization of our drugs, including KYNAMRO.

Many of our competitors have substantially greater financial, technical and human resources than we do. In addition, many of these competitors have significantly greater experience than we do in conducting preclinical testing and human clinical studies of new pharmaceutical products and in obtaining FDA and other regulatory approvals of products for use in health care. Accordingly, our competitors may succeed in obtaining regulatory approval for products earlier than we do. Marketing and sales capability is another factor relevant to the competitive position of our drugs, and we will rely on our partners to provide this capability.

Regarding KYNAMRO, some competitors are pursuing a development or commercialization strategy that competes with our strategy for KYNAMRO. Other companies are currently developing products that could compete with KYNAMRO. Products such as microsomal triglyceride transfer protein inhibitors, or MTP inhibitors, and other lipid lowering drugs other companies are developing or commercializing could potentially compete with KYNAMRO. For example, Aegerion Pharmaceuticals, Inc. received approval from the FDA to market its MTP inhibitor, lomitapide, as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol, total cholesterol, apolipoprotein B and non-high-density-lipoprotein cholesterol in patients with HoFH. Aegerion has also submitted a marketing authorization application for lomitapide to the European Medicines Agency seeking approval of lomitapide as an adjunct to a low fat diet and other lipid-lowering therapies to reduce cholesterol in patients with HoFH, and has received an opinion from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency recommending the marketing authorization for lomitapide. Our revenues and financial position will suffer if KYNAMRO cannot compete effectively in the marketplace.

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

Following approval of a drug, we and our partners must comply with comprehensive government regulations regarding the manufacture, marketing and distribution of drug products. Even if approved, we or our partners may not obtain the labeling claims necessary or desirable for successfully commercializing our drug products, including KYNAMRO.

The FDA and foreign regulatory authorities have the authority to impose significant restrictions on an approved drug product through the product label and on advertising, promotional and distribution activities. For example:

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



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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.

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

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

We entered into this collaboration primarily to:

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

In general, we cannot control the amount and timing of resources that Genzyme devotes to our collaboration. If Genzyme fails to further develop and commercialize KYNAMRO, or if Genzyme's efforts are not effective, our business may be negatively affected. We are relying on Genzyme to obtain additional marketing approvals for and successfully commercialize KYNAMRO. Our collaboration with Genzyme may not continue or result in the successful commercialization of KYNAMRO. Genzyme can terminate our collaboration at any time. If Genzyme stopped developing or commercializing KYNAMRO, we would have to seek additional sources for funding and may have to delay or reduce our development and commercialization programs for

KYNAMRO. If Genzyme does not successfully commercialize KYNAMRO, we may receive limited or no revenues for KYNAMRO. In addition, Sanofi's acquisition of Genzyme could disrupt Genzyme or distract it from performing its obligations under our collaboration.

**If Genzyme cannot manufacture finished drug product for KYNAMRO or the post-launch supply of the active drug substance for KYNAMRO, KYNAMRO may not achieve or maintain commercial success.**

We rely on Genzyme to manufacture the finished drug product for KYNAMRO, including the initial commercial launch supply. In addition, Genzyme is responsible for the long term supply of both KYNAMRO drug substance and finished drug product. Genzyme may not be able to reliably manufacture KYNAMRO drug substance and drug product to support the long term commercialization of KYNAMRO. If Genzyme cannot reliably manufacture KYNAMRO drug substance and drug product, KYNAMRO may not achieve or maintain commercial success, which will harm our ability to generate revenue.

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

We cannot guarantee that any of our drugs will be safe and effective, or will be approved for commercialization. In addition, we cannot guarantee that KYNAMRO will be approved outside the United States or for additional indications. We and our partners must conduct time-consuming, extensive and costly clinical studies to show the safety and efficacy of each of our drugs, including KYNAMRO, before a drug can be approved for sale. We must conduct these studies in compliance with FDA regulations and with comparable regulations in other countries.

We and our partners may not obtain necessary regulatory approvals on a timely basis, if at all, for any of our drugs. It is possible that other regulatory agencies will not approve KYNAMRO for marketing. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of any of our drugs, including KYNAMRO, the agency will not approve the specific drug or will require additional studies, which can be time consuming and expensive and which will delay or harm commercialization of the drug. For example, in March 2013 the CHMP of the European Medicines Agency maintained a negative opinion for Genzyme's marketing authorization application for KYNAMRO as a treatment for patients with HoFH.

Failure to receive marketing approval for our drugs, including KYNAMRO outside the United States, or delays in these approvals could prevent or delay commercial introduction of the drug, and, as a result, could negatively impact our ability to generate revenue from product sales.



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**If the results of clinical testing indicate that any of our drugs are not suitable for commercial use we may need to abandon one or more of our drug development programs.**

Drug discovery and development has inherent risks and the historical failure rate for drugs is high. Antisense drugs are a relatively new approach to therapeutics. If we cannot demonstrate that our drugs are safe and effective for human use, we may need to abandon one or more of our drug development programs. There are ongoing clinical studies for KYNAMRO and sales to patients, adverse events from which could negatively impact our pending or planned marketing approval applications and commercialization of KYNAMRO.

In the past, we have invested in clinical studies of drugs that have not met the primary clinical end points in their Phase 3 studies. Similar results could occur in any additional clinical studies for KYNAMRO and in clinical studies for our other drugs. If any of our drugs in clinical studies, including KYNAMRO, does not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for the drug and our stock price could decline.

**Even if our drugs are successful in preclinical and human clinical studies, the drugs may not be successful in late-stage clinical studies.**

Successful results in preclinical or initial human clinical studies, including the Phase 3 results for KYNAMRO and the Phase 2 results for some of our other drugs in development, may not predict the results of subsequent clinical studies, including subsequent studies of KYNAMRO. There are a number of factors that could cause a clinical study to fail or be delayed, including:

- the clinical study may produce negative or inconclusive results;
- regulators may require that we hold, suspend or terminate clinical research for noncompliance with regulatory requirements;
- we, our partners, the FDA or foreign regulatory authorities could suspend or terminate a clinical study due to adverse side effects of a drug on subjects in the trial;
- we may decide, or regulators may require us, to conduct additional preclinical testing or clinical studies;
- enrollment in our clinical studies may be slower than we anticipate;
- the cost of our clinical studies may be greater than we anticipate; and
- the supply or quality of our drugs or other materials necessary to conduct our clinical studies may be insufficient, inadequate or delayed.

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

**If we cannot manufacture our drugs or contract with a third party to manufacture our drugs at costs that allow us to charge competitive prices to buyers, we cannot market our products profitably.**

To successfully commercialize any of our drugs, we or our partner would need to establish large-scale commercial manufacturing capabilities either on our own or through a third party manufacturer. In addition, as our drug development pipeline increases and matures, we will have a greater need for clinical trial and commercial manufacturing capacity. We have limited experience manufacturing pharmaceutical products of the chemical class represented by our drugs, called oligonucleotides, on a commercial scale for the systemic administration of a drug. There are a small number of suppliers for certain capital equipment and raw materials that we use to manufacture our drugs, and some of these suppliers will need to increase their scale of production to meet our projected needs for commercial manufacturing. Further, we must continue to improve our manufacturing processes to allow us to reduce our drug costs. We may not be able to manufacture our drugs at a cost or in quantities necessary to make commercially successful products.

Also, manufacturers, including us, must adhere to the FDA's current Good Manufacturing Practices regulations and similar regulations in foreign countries, which the applicable regulatory authorities enforce through facilities inspection programs. We and our contract manufacturers may not comply or maintain compliance with Good Manufacturing Practices, or similar foreign regulations. Non-compliance could significantly delay or prevent receipt of marketing approval for our drugs, including KYNAMRO, or result in enforcement action after approval that could limit the commercial success of our drugs, including KYNAMRO.



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**We depend on third parties to conduct our clinical studies for our drugs and any failure of those parties to fulfill their obligations could adversely affect our development and commercialization plans.**

We depend on independent clinical investigators, contract research organizations and other third-party service providers to conduct our clinical studies for our drugs and expect to continue to do so in the future. For example, Medpace is the primary clinical research organization for the ongoing clinical studies for KYNAMRO. We rely heavily on these parties for successful execution of our clinical studies, but do not control many aspects of their activities. For example, the investigators are not our employees. However, we are responsible for ensuring that these third parties conduct each of our clinical studies in accordance with the general investigational plan and approved protocols for the study. Third parties may not complete activities on schedule, or may not conduct our clinical studies in accordance with regulatory requirements or our stated protocols. The failure of these third parties to carry out their obligations or a termination of our relationship with these third parties could delay or prevent the development, approval and commercialization of our drugs, including any expanded product label for KYNAMRO.

## Risks Associated with our Businesses as a Whole

**We have incurred losses, and our business will suffer if we fail to consistently achieve profitability in the future.***

Because drug discovery and development requires substantial lead-time and money prior to commercialization, our expenses have generally exceeded our revenue since we were founded in January 1989. As of June 30, 2013, we had an accumulated deficit of approximately $918.8 million and stockholders' equity of approximately $401.1 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from research grants and the sale or licensing of our patents, as well as interest income. We may incur additional operating losses over the next several years, and these losses may increase if we cannot increase or sustain revenue. We may not successfully develop any additional products or achieve or sustain future profitability.

**Since corporate partnering is a key part of our strategy to fund the development and commercialization of our development programs, if any of our collaborative partners fail to fund our collaborative programs, or if we cannot obtain additional partners, we may have to delay or stop progress on our drug development programs.***

To date, corporate partnering has played a key role in our strategy to fund our development programs and to add key development resources. We plan to continue to rely on additional collaborative arrangements to develop and commercialize our unpartnered drugs. However, we may not be able to negotiate favorable collaborative arrangements for these drug programs. If we cannot continue to secure additional collaborative partners, our revenues could decrease and the development of our drugs could suffer.

Our corporate partners are developing and/or funding many of the drugs in our development pipeline, including AstraZeneca, ATL, Atlantic Pharmaceuticals, Biogen Idec, iCo, Genzyme, GSK, OncoGenex, Pfizer, Teva Pharmaceutical Industries Ltd., and Xenon. If any of these pharmaceutical companies stops developing and/or funding these drugs, our business could suffer and we may not have, or be willing to dedicate, the resources available to develop these drugs on our own.

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

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

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

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

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

For example, a collaborator such as AstraZeneca, Biogen Idec, Genzyme, or GSK, could determine that it is in its financial interest to:

- pursue alternative technologies or develop alternative products that may be competitive with the drug that is part of the collaboration with us;
- pursue higher-priority programs or change the focus of its own development programs; or
- choose to devote fewer resources to our drugs than it does for its own drugs.

If any of these occur, it could affect our partner's commitment to the collaboration with us and could delay or otherwise negatively affect the commercialization of our drugs, including KYNAMRO.

**If we do not progress in our programs as anticipated, the price of our securities could decrease.***

For planning purposes, we estimate and may disclose the timing of a variety of clinical, regulatory and other milestones, such as when we anticipate a certain drug will enter the clinic, when we anticipate completing a clinical study, or when we anticipate filing an application for marketing approval. We base our estimates on present facts and a variety of assumptions. Many underlying assumptions are outside of our control. If we do not achieve milestones in accordance with our or our investors' expectations, including milestones for additional approvals or sales expectations of KYNAMRO, the price of our securities would likely decrease.

For example, in March 2013 the CHMP of the European Medicines Agency maintained a negative opinion for Genzyme's marketing authorization application for 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. This lawsuit may be costly and may not be resolved in our favor.

If a third party claims that our drugs or technology infringe its patents or other intellectual property rights, we may have to discontinue an important product or product line, alter our products and processes, pay license fees or cease certain activities. We may not be able to obtain a license to needed intellectual property on favorable terms, if at all. There are many patents issued or applied for in the biotechnology industry, and we may not be aware of patents or patent applications held by others that relate to our business. This is especially true since patent applications in the United States are filed confidentially for the first 18 months. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain unresolved.

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

Many of our drugs are undergoing clinical studies or are in the early stages of research and development. All of our drug programs will require significant additional research, development, preclinical and/or clinical testing, regulatory approval and/or commitment of significant additional resources prior to their successful commercialization. As of June 30, 2013, we had cash, cash equivalents and short-term investments equal to $590.8 million. If we do not meet our goals to commercialize KYNAMRO or our other drugs, or to license our drugs and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:





- additional marketing approvals and successful commercial launch of KYNAMRO;
- changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements;
- continued scientific progress in our research, drug discovery and development programs;
- the size of our programs and progress with preclinical and clinical studies;
- the time and costs involved in obtaining regulatory approvals;
- competing technological and market developments, including the introduction by others of new therapies that address our markets; and

- the profile and launch timing of our drugs.

If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available at all or on acceptable terms. If we raise additional funds by issuing equity securities, the shares of existing stockholders will be diluted and the price, as well as the price of our other securities, may decline. If adequate funds are not available or not available on acceptable terms, we may have to cut back on one or more of our research, drug discovery or development programs. For example, in January 2005 we terminated the development of two lower priority drugs, ISIS 14803 and ISIS 104838. Alternatively, we may obtain funds through arrangements with collaborative partners or others, which could require us to give up rights to certain of our technologies or drugs.

**The loss of key personnel, or the inability to attract and retain highly skilled personnel, could make it more difficult to run our business and reduce our likelihood of success.**

We are dependent on the principal members of our management and scientific staff. We do not have employment agreements with any of our executive officers that would prevent them from leaving us. The loss of our management and key scientific employees might slow the achievement of important research and development goals. It is also critical to our success that we recruit and retain qualified scientific personnel to perform research and development work. We may not be able to attract and retain skilled and experienced scientific personnel on acceptable terms because of intense competition for experienced scientists among many pharmaceutical and health care companies, universities and non-profit research institutions. In addition, failure to succeed in clinical studies may make it more challenging to recruit and retain qualified scientific personnel.

**If the price of our securities continues to be highly volatile, this could make it harder for you to liquidate your investment and could increase your risk of suffering a loss.**

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding June 30, 2013, the market price of our common stock ranged from $7.56 to $28.66 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, 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.



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**Because we use biological materials, hazardous materials, chemicals and radioactive compounds, if we do not comply with laws regulating the protection of the environment and health and human safety, our business could be adversely affected.**

Our research, development and manufacturing activities involve the use of potentially harmful biological materials as well as materials, chemicals and various radioactive compounds that could be hazardous to human health and safety or the environment. We store these materials and various wastes resulting from their use at our facilities in Carlsbad, California pending ultimate use and disposal. We cannot completely eliminate the risk of contamination, which could cause:

- interruption of our research, development and manufacturing efforts;
- injury to our employees and others;
- environmental damage resulting in costly clean up; and
- liabilities under federal, state and local laws and regulations governing health and human safety, as well as the use, storage, handling and disposal of these materials and resultant waste products.

In such an event, we may be held liable for any resulting damages, and any liability could exceed our resources. Although we carry insurance in amounts and types that we consider commercially reasonable, we do not have insurance coverage for losses relating to an interruption of our research, development or manufacturing efforts caused by contamination, and the coverage or coverage limits of our insurance policies may not be adequate. If our losses exceed our insurance coverage, our financial condition would be adversely affected.

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

Regulus is a company that we and Alnylam established to focus on discovering, developing, and commercializing microRNA therapeutics. We exclusively licensed to Regulus our intellectual property rights covering microRNA technology. Regulus operates as an independent company and Regulus and its employees are ultimately responsible for researching and developing our microRNA technology. If Regulus is not successful, the value of our microRNA technology would be harmed and we would lose part or all of our investment in Regulus. In addition, Regulus' directors, executive management team, and strategic partners, including Alnylam, Isis, AstraZeneca, GSK, Biogen Idec and Sanofi have agreed that until October 4, 2013, 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.

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

We manufacture our research and clinical supplies in a manufacturing facility located in Carlsbad, California. The facilities and the equipment we use to research, develop and manufacture our drugs would be costly to replace and could require substantial lead time to repair or replace. Our facilities may be harmed by natural or man-made disasters, including, without limitation, earthquakes, floods, fires and acts of terrorism; and if our facilities are affected by a disaster, our development and commercialization efforts would be delayed. Although we possess insurance for damage to our property and the disruption of our business from casualties, this insurance may not be sufficient to cover all of our potential losses and may not continue to be available to us on acceptable terms, or at all.

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

Our certificate of incorporation provides for classified terms for the members of our board of directors. Our certificate also includes a provision that requires at least 66 ²¤₃ percent of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15 percent or more of our voting stock, except in cases where certain directors approve the transaction or certain minimum price criteria and other procedural requirements are met.

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.



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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.

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

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

## ITEM 4. CONTROLS AND PROCEDURES

As of the end of the period covered by this Quarterly Report on Form 10-Q, we carried out an evaluation, under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended. We conducted our evaluation following the 1992 Internal Control—Integrated Framework set forth by the Committee of Sponsoring Organizations of the Treadway Commission. Based on this evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of June 30, 2013. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to June 30, 2013.

An evaluation was also performed under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of any change in our internal control over financial reporting that occurred during our last fiscal quarter and that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting. That evaluation did not identify any change in our internal control over financial reporting that occurred during our latest fiscal quarter and that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

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



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# PART II — OTHER INFORMATION

## ITEM 1. LEGAL PROCEEDINGS

In September 2011, we filed a patent infringement lawsuit against Santaris Pharma A/S and Santaris Pharma A/S Corp. in the United States District Court of the Southern District of California. Our infringement lawsuit alleges that Santaris' activities providing antisense drugs and antisense drug discovery services to several pharmaceutical companies infringes U.S. Patent No. 6,326,199, entitled "Gapped 2' Modified Oligonucleotides" and U.S. Patent No. 6,066,500, entitled "Antisense Modulation of Beta Catenin Expression." In the lawsuit we are seeking monetary damages and an injunction enjoining Santaris from conducting or participating in the infringing activities. In December 2011, Santaris filed an answer to our complaint, denying our allegations, and seeking a declaration from the court that Santaris has not, and does not, infringe the patents we asserted against Santaris in the suit. In January 2012, Santaris filed a motion for summary judgment asking the court to decide as a matter of law that Santaris' activities do not infringe the patents we assert in the suit. In September 2012, the court denied Santaris' motion for summary judgment and opened limited discovery related to whether Santaris' alleged infringing activities are permitted by the safe harbor under 35 U.S.C. Section 271(e)(1). In April 2013, we amended our complaint related to the lawsuit to include additional claims alleging that Santaris' activities providing antisense drugs and antisense drug discovery services to a pharmaceutical company infringes U.S. Patent No. 6,440,739 entitled "Antisense Modulation of Glioma-Associated Oncogene-2 Expression"; and that Santaris induced its actual and prospective pharmaceutical partners to infringe U.S. Patent No. 6,326,199.

## 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

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**ITEM 6. EXHIBITS**

a. Exhibits

| Exhibit Number | Description of Document |
|---|---|
| 10.1 | HTT Research, Development, Option and License Agreement dated April 8, 2013 among the Registrant, F. Hoffman-La Roche Ltd and Hoffman-La Roche Inc. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. |
| 10.2 | Letter Agreement dated April 8, 2013 between the Registrant and CHDI Foundation, Inc. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. |
| 31.1 | Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002. |
| 31.2 | Certification by Chief Financial Offic5er Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002. |
| 32.1 | Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002. |
| 101 | The following financial statements from the Isis Pharmaceuticals, Inc. Quarterly Report on Form 10-Q for the quarter ended June 30, 2013, formatted in Extensive Business Reporting Language (XBRL): (i) condensed consolidated balance sheets, (ii) condensed consolidated statements of operations, (iii) condensed consolidated statements of comprehensive income (loss), (iv) condensed consolidated statements of cash flows and (v) notes to condensed consolidated financial statements (detail tagged). |

**Isis Pharmaceuticals, Inc.**

(Registrant)



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**SIGNATURES**

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

| Signatures | Title | Date |
|---|---|---|
| /s/ Stanley T. Crooke<br>Stanley T. Crooke, M.D., Ph.D. | Chairman of the Board, President, and Chief Executive Officer<br>(Principal executive officer) | August 6, 2013 |
| /s/ Elizabeth L. Hougen<br>Elizabeth L. Hougen | Senior Vice President, Finance and Chief Financial Officer<br>(Principal financial and accounting officer) | August 6, 2013 |

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

# HTT RESEARCH, DEVELOPMENT, OPTION AND LICENSE AGREEMENT

**AMONG**

**ISIS PHARMACEUTICALS, INC.,**

**AND**

**F. HOFFMANN-LA ROCHE LTD**

**AND**

**HOFFMANN-LA ROCHE INC.**

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This HTT RESEARCH, DEVELOPMENT, OPTION AND LICENSE AGREEMENT (the "***Agreement***") is entered into as of the 8th day of April, 2013 (the "***Effective Date***") by and among **ISIS PHARMACEUTICALS, INC.**, a Delaware corporation, having its principal place of business at 2855 Gazelle Court, Carlsbad, California 92010 ("***Isis***"), and **F. HOFFMANN-LA ROCHE LTD**, a Swiss corporation, having its principal place of business at Grenzacherstrasse 124, 4070 Basel, Switzerland ("***Roche Basel***") and **HOFFMANN-LA ROCHE INC.**, a New Jersey corporation, having its principal place of business at 340 Kingsland Street, Nutley, New Jersey 07110 ("***Roche Nutley***"; Roche Basel and Roche Nutley are collectively referred to as "***Roche***"). Roche and Isis each may be referred to herein individually as a "***Party***" or collectively as the "***Parties***." Capitalized terms used in this Agreement, whether used in the singular or the plural, have the meaning set forth in APPENDIX 1. All attached appendices and schedules are a part of this Agreement.

## RECITALS

**WHEREAS**, Isis has expertise in discovering and developing antisense drugs, and is researching compounds to identify and select a drug to treat Huntington's Disease;

**WHEREAS**, Roche has expertise in developing and commercializing drugs, and Roche is interested in researching, developing and commercializing an antisense drug to treat Huntington's Disease;

**WHEREAS**, Roche and Isis desire to conduct research activities to identify and select at least one antisense drug to treat Huntington's Disease;

**WHEREAS**, Roche and Isis also desire to conduct a research collaboration focused on discovering an antisense drug to treat Huntington's Disease using Roche's Brain Shuttle technology designed to deliver drugs through the blood-brain barrier;

**WHEREAS**, the Parties anticipate they will conduct the research programs in parallel with and without using Roche's Brain Shuttle technology, recognizing that Isis' non-Brain Shuttle program is further along in the research and development process, and that drugs from either or both program(s) may move forward in development based on emergent data and the commercial market of the individual drugs; and

**WHEREAS**, Roche desires Isis to develop the HTT drug through completion of the initial Phase 1 Trial and grant Roche an option to obtain an exclusive license to develop and commercialize such drug;

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



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## ARTICLE 1.
## RESEARCH AND DEVELOPMENT

**1.1.** **Overview**. The intent of the Collaboration is for the Parties to conduct two research programs in parallel focused on (i) an Isis HTT program initially centered around the research of Allele Selective Compounds and Non-Allele Selective Compounds to designate an Isis Development Candidate, and (ii) a collaborative HTT program between Isis and Roche, funded by Roche, involving Roche's proprietary technology designed to enhance delivery of molecules through the blood-brain barrier ("***Brain Shuttle***"), where the Parties will combine an Isis Compound with such Brain Shuttle technology to develop a Brain Shuttle Development Candidate. From the Effective Date until the date the Option is exercised, expires or is terminated (the "***Option Period***"), Isis will Develop and fund the initial Isis Development Candidate through the first Phase 1 Trial, and Roche will have an Option to obtain an exclusive license to further Develop and Commercialize the Development Candidates. Drugs from either or both program(s) may move forward in development based on data and the commercial market of the individual drugs. If Roche exercises its Option, Roche will be responsible for all further pre-clinical, clinical, regulatory, manufacturing and commercial activities related to Products. The purpose of this Section 1.1 is to provide a high-level overview of the roles, responsibilities, rights and obligations of each Party under this Agreement with regard to the R&D Plans and Products, and therefore this Section 1.1 is qualified in its entirety by the more detailed provisions of this Agreement set forth below.

**1.2.** **Isis Development Candidate-R&D Plan**.

**1.2.1.** **Isis Development Candidate-R&D Plan Activities**. The Isis Development Candidate-R&D Plan is attached hereto as APPENDIX 2, and sets forth the research and development activities the Parties will conduct during the Option Period with the first Compound designated an Isis Development Candidate, and through completion of the Registration-Directed Trials. As of the Effective Date, the Isis Development Candidate-R&D Plan focuses primarily on the research and Development of Non-Allele Selective Compounds, and is intended to achieve designation of one Isis Development Candidate and one Back-Up Compound. If the Parties subsequently decide to expand the efforts under such plan on the research and Development of Allele Selective Compounds, the Parties will mutually agree on any appropriate changes to the Isis Development Candidate-R&D Plan, with Roche being responsible for the incremental cost of any such changes.

**1.2.2.** **Conducting the Isis Development Candidate-R&D Plan**. During the Option Period, Roche and Isis will each use Commercially Reasonable Efforts to conduct the research and Development activities designated for each of them, respectively under the Isis Development Candidate-R&D Plan in accordance with the timelines specified therein, giving due consideration to the recommendations and advice of the JSC; *provided*, neither Roche nor Isis will have any obligation to perform any activity that, after having consulted the JSC, it in good faith believes



that continuing such activity would violate any Applicable Law, ethical principles, or principles of scientific integrity.

**1.2.3.** **Isis' Performance Milestones**. During the Option Period, Isis will use Commercially Reasonable Efforts to:

**(a)** Designate at least one Isis Development Candidate by [***]; *provided*, *however*, that if research or Development issues arise that are outside of Isis' reasonable control and make such designation by such date impossible, the Parties will negotiate in good faith to revise the date by which Isis may designate an Isis Development Candidate;

**(b)** Within [***] designating an Isis Development Candidate, complete the [***] for such Isis Development Candidate; and

**(c)** Within [***] are completed for an Isis Development Candidate and Isis has obtained the [***], [***], [***] and [***] data generated from such [***] sufficient to support the [***], [***] for such Isis Development Candidate.

**1.2.4.** **Notice of Isis Development Candidate Designation**. When Isis first designates an Isis Development Candidate, Isis will notify Roche in writing promptly after such designation and, together with such notice, will provide Roche the applicable Development Candidate Data Package.

**1.2.5.** **Isis Development Candidate IND-Enabling Toxicology Studies**. Once available to Isis, Isis will promptly deliver to Roche the pharmacology, toxicology, histology and pharmacokinetic data generated from the IND-Enabling Toxicology Studies under the Isis Development Candidate-R&D Plan.

**1.2.6.** **Phase 1 Trial**. Isis will keep the JSC informed of the progress of the Phase 1 Trial. Once available to Isis, Isis will promptly deliver to Roche the applicable Phase 1 Trial Data Package.

**1.2.7.** [*******]. Prior to the Initiation of the [***] for the Isis Development Candidate, the Parties will discuss and mutually agree on whether to conduct an [***] for such Isis Development Candidate. If the Parties mutually agree to conduct such an [***], then the [***] will be considered an Approved Change to the Isis Development Candidate-R&D Plan and the costs to conduct such [***] will be treated as Additional Costs in accordance with Section 1.6.1(b).

**1.3.** **Conducting the Brain Shuttle Development Candidate-R&D Plan**. In addition to the Isis Development Candidate-R&D Plan performed under Section 1.2 above, Roche and Isis will conduct a research collaboration under the Brain Shuttle Development Candidate-R&D Plan to identify a Brain Shuttle Development Candidate. The Brain Shuttle Development Candidate-R&D Plan is attached hereto as APPENDIX 3 and sets forth the research activities the Parties will conduct through designation of the Brain



Shuttle Development Candidate. Once the first Brain Shuttle Development Candidate is designated, Roche will update the Brain Shuttle Development Candidate-R&D Plan to cover Development activities for the first Brain Shuttle Development Candidate through the completion of Registration-Directed Trials, which plan will be consistent with the level of effort and diligence set forth in the Isis Development Candidate-R&D Plan. Changes to the Brain Shuttle Development Candidate-R&D Plan that affect the Isis R&D Activities thereunder must be unanimously agreed to by the JSC or, if the JSC no longer exists, by the Parties. Roche and Isis will each use Commercially Reasonable Efforts to conduct the research and Development activities designated for each of them, respectively under the Brain Shuttle Development Candidate-R&D Plan in accordance with the timelines specified therein, giving due consideration to the recommendations and advice of the JSC; *provided*, neither Roche nor Isis will have any obligation to perform any activity that, after having consulted the JSC, it in good faith believes that continuing such activity would violate any Applicable Law, ethical principles, or principles of scientific integrity.

**1.3.1.** **Brain Shuttle Development Candidate Designation**. If Roche, after consultation with the JSC, determines a Compound under the Brain Shuttle Development Candidate-R&D Plan is ready to start IND-Enabling Toxicology Studies, such Compound will be a "***Brain Shuttle Development Candidate***."

**1.3.2.** **Brain Shuttle Development Candidate IND-Enabling Toxicology Studies**. Once available to Roche, Roche will promptly deliver to Isis the pharmacology, toxicology, histology and pharmacokinetic data generated from the IND-Enabling Toxicology Studies under the Brain Shuttle Development Candidate-R&D Plan.

**1.3.3.** **Phase 1 Trial**. Roche will use Commercially Reasonable Efforts to conduct the Phase 1 Trial for the Brain Shuttle Development Candidate under the Brain Shuttle Development Candidate-R&D Plan. Roche will keep Isis informed of the progress of each Phase 1 Trial through the JSC.

**1.4.** **Disclosure of Results**. Each Party will promptly disclose to the other Party via disclosure at JSC meetings the results of work performed by such Party under each R&D Plan. Isis and Roche will provide reports and analyses at each JSC meeting, and more frequently on reasonable request by the JSC, detailing the current status of each R&D Plan. If the JSC has dissolved, then each Party will promptly disclose such data and results directly to the other Party.

**1.5.** **Development Management**.

**1.5.1.** **JSC**. The Parties will establish a joint steering committee (the "***JSC***") to provide advice and make recommendations on the conduct of the Collaboration consistent with the R&D Plans. The JSC will act as a forum for sharing information about the activities conducted by the Parties hereunder, as an advisory body, and will have decision-making authority to the extent set forth on SCHEDULE 1.5.1. The JSC will consist of two (2) qualified representatives appointed by Isis, and two (2) qualified representatives appointed by Roche. Prior to Option exercise, Isis will



designate one of its representatives to act as the chairperson of the JSC. After Option exercise, Roche will designate one of its representatives to act as the chairperson of the JSC. The chairperson will be responsible for overseeing the activities of the JSC. SCHEDULE 1.5.1 sets forth certain JSC governance matters. The JSC will determine the JSC operating procedures at its first meeting, which will be codified in the written minutes of the first JSC meeting. In addition, during the term of the JSC, CHDI will have the right to participate in JSC meetings as a non-voting observer; *provided, however*, if Isis and Roche reasonably determine in good faith after discussion with CHDI that, due to participation in programs with a potentially competitive drug, CHDI should no longer participate in JSC meetings and be exposed to program data, then Isis will provide CHDI with written notice of such determination and thereafter CHDI will no longer participate in meetings of the JSC. The CHDI observer shall be a person reasonably acceptable to both Roche and Isis.

**1.5.2.** **Decision Making**.

**(a)** ***Under the Isis Development Candidate-R&D Plan***. Prior to Option exercise, except as provided below in Section 1.5.2(b), Isis will have the final decision-making authority regarding the conduct of the Isis Development Candidate-R&D Plan, and whether to accept and how to implement the JSC's recommendations.

**(b)** ***With Respect to All Subsequent Isis Development Candidates***. For the second and any subsequent Isis Development Candidates, subject to Section 1.5.2(e), Roche will have the final decision-making authority regarding whether to Initiate the IND-Enabling Toxicology Studies and all subsequent Development activities thereafter. If the first Compound designated an Isis Development Candidate is no longer being Developed, then the next Compound designated an Isis Development Candidate that takes its place will still be considered the "first" Isis Development Candidate for purposes of this Section 1.5.2(b), and the Isis Development Candidate-R&D Plan will be amended accordingly as mutually agreed by the Parties to cover any research and Development activities and related costs for such replacement Isis Development Candidate in accordance with Section 1.8 below.

**(c)** ***Under the Brain Shuttle Development Candidate-R&D Plan***. Subject to Section 5.1 and Section 1.5.2(e), Roche will have the final decision-making authority regarding selection of Brain Shuttle Development Candidates, the conduct of the Brain Shuttle Development Candidate-R&D Plan, and whether to accept and how to implement the JSC's recommendations.

**(d)** ***Development Decision Making After Option Exercise***. After Option exercise and without limiting Roche's obligations under this Agreement to use Commercially Reasonable Efforts, Roche will have the final



decision making authority for which Products to Initiate Phase 2 and all subsequent Clinical Trials. In addition, Roche will have full responsibility for designing, conducting, funding and implementing the further Development of Products, including clinical trials and regulatory submissions.

**(e)** ***Exceptions***. If Roche's exercise of its decision-making authority pursuant to Section 1.5.2(b), Section 1.5.2(c) or Section 1.5.2(d) would increase costs for any Isis R&D Activities, then such decision must be unanimously agreed to by the JSC or, if the JSC no longer exists, by the Parties.

**1.5.3.** **Alliance Managers**. Each Party will appoint a representative to act as its alliance manager (each, an "***Alliance Manager***"). Each Alliance Manager will be responsible for supporting the JSC and performing the activities listed in SCHEDULE 1.5.3.

**1.6.** **Collaboration Costs and Expenses**.

**1.6.1.** **Isis Development Candidate-R&D Plan**.

**(a)** **Isis Development Candidate-R&D Plan Costs — Generally**. During the Option Period, except as otherwise provided under Section 1.6.1(b), Isis will be responsible for all costs and expenses associated with the Isis R&D Activities designated under the Isis Development Candidate-R&D Plan for the first Compound designated an Isis Development Candidate, and Roche will be responsible for all costs and expenses associated with any Roche R&D Activities designated under the Isis Development Candidate-R&D Plan. Isis cannot change any of the Roche R&D Activities without the unanimous agreement of the JSC or, if

the JSC no longer exists, Roche. As provided in Section 1.8, Roche is responsible for the costs of any research and Development activities for an Additional Isis Development Candidate.

**(b)** **Additional Costs Associated with Approved Changes to the Isis Development Candidate-R&D Plan**. Roche will be responsible for paying Isis quarterly in advance for any Additional Costs resulting from Approved Changes. Roche will review and approve the Additional Costs before any Approved Changes are implemented by Isis. Isis and Roche will update the Isis Development Candidate-R&D Plan to reflect any such Approved Changes and Isis will invoice Roche for any such Additional Costs quarterly in advance after such Additional Costs are approved. Isis may reasonably estimate its FTE time required to perform the Approved Changes. Roche will pay the invoices submitted pursuant to this Section 1.6.1(b) for such approved Additional Costs within thirty (30) days after Roche's receipt of the applicable invoice. Isis will use its Commercially Reasonable Efforts to complete Approved Changes



within the amount of the agreed Additional Costs. If at any time during the performance of the Approved Changes, Isis expects its actual Additional Costs to be greater than [***] of the previously agreed Additional Costs for a particular Approved Change(s) (the difference being "***Change Overruns***"), then Isis shall promptly notify the JSC which will then discuss and agree whether the Approved Changes should continue, and if so, how the Parties shall share the cost of any Change Overruns. Any Change Overruns Roche agrees to pay will be considered Additional Costs. Unless approved by Roche, Roche will not be responsible for Change Overruns that are greater than [***] of the previously agreed Additional Costs for a particular Approved Change(s).

**(c)** **Reconciliation of Any Overpayment or Underpayment of Additional Costs**. At the end of every second (2nd) and fourth (4th) Calendar Quarter during any period where Additional Costs are incurred (and again at the completion of all of the Approved Changes), Isis will provide Roche with an accounting of actual costs incurred by Isis (including Isis' estimated FTE costs) compared to the Additional Costs paid in advance by Roche. After such accounting, if Isis' actual costs incurred were greater than the Additional Costs paid in advance by Roche, then Roche will pay Isis the amount of such difference within thirty (30) days after Isis provides the accounting to Roche and Roche's receipt of an invoice from Isis. If, however, after such accounting Isis' actual costs incurred were less than the Additional Costs paid in advance by Roche, then Isis will provide Roche the amount of such difference in the form of a credit against the next payment (including any future payments for any then ongoing Approved Changes) to be paid by Roche to Isis under this Agreement.

**1.6.2.** **Brain Shuttle Development Candidate-R&D Plan**.

**(a)** **Brain Shuttle Development Candidate-R&D Plan Costs**. Roche will be responsible for all costs and expenses associated with the Brain Shuttle Development Candidate-R&D Plan, including pre-clinical *in vitro* or *in vivo* efficacy studies costs, manufacturing costs, IND-Enabling Toxicology Study costs, chronic toxicology study costs, clinical trial costs (including OLE Trial costs), and all costs and expenses associated with the Isis R&D Activities and the Roche R&D Activities designated under the Brain Shuttle Development Candidate-R&D Plan.

**(b)** **Brain Shuttle Development Candidate-R&D Plan — Cost Estimates and Invoicing**.

**(i)** ***Brain Shuttle Program Cost Estimate***. Roche will pay Isis in advance on a quarterly basis for Isis' performance of the Isis R&D Activities designated under the Brain Shuttle Development



Candidate-R&D Plan to progress to the next significant stage of research or development at the then-applicable Isis FTE Rate, plus any reasonable out-of-pocket expenses incurred by Isis in performing such work. The costs of ASOs to be supplied by Isis under the Brain Shuttle Development Candidate-R&D Plan will be calculated in accordance with SCHEDULE 1.6.2(b)(i). Isis may reasonably estimate its FTE time required to perform the Isis R&D Activities designated under the Brain Shuttle Development Candidate-R&D Plan. Each time the Parties agree to, or expand, the Isis R&D Activities under the Brain Shuttle Development Candidate-R&D Plan, Isis will provide Roche with a good faith estimate of the internal and external costs (each such estimate, a "***Brain Shuttle Program Cost Estimate***") to conduct such Isis R&D Activities to the end of the next significant stage of research or development, and Isis and Roche will endeavor to mutually agree on a final Brain Shuttle Program Cost Estimate.

**(ii)** ***Payment Schedule and Invoicing; Reconciliation of Any Overpayment or Underpayment of Additional Costs***. Once a given Brain Shuttle Program Cost Estimate is finalized under Section 1.6.2(b)(i) and Isis is ready to start such work, Isis will deliver to Roche each quarter in advance an invoice for Isis' estimated costs for the coming Calendar Quarter. Roche will pay Isis within thirty (30) days after receiving such invoice. Isis will use its Commercially Reasonable Efforts to complete the Isis R&D Activities related to a given Brain Shuttle Program Cost Estimate within the amount of the agreed Brain Shuttle Program Cost Estimate. For each Brain Shuttle Program Cost Estimate, Isis and Roche will handle any cost overruns and reconciliations of any overpayment or underpayment of Additional Costs using the same process used under Section 1.6.1(b) and Section 1.6.1(c) above.

**1.7.** **Manufacturing and Supply**.

**1.7.1.** **Isis Development Candidate-R&D Plan**.

**(a)** **Supplies for Activities During the Option Period**. During the Option Period, [***], for the first Compound designated an Isis Development Candidate, Isis will supply API, finished Product and any research-grade Compound sufficient to support the Isis

R&D Activities designated under the Isis Development Candidate-R&D Plan. In addition, during the Option Period, for the first Compound designated an Isis Development Candidate, Isis will supply API, finished Product, and research-grade Compound sufficient to support any Roche R&D Activities designated under the Isis Development Candidate-R&D Plan, and Isis will provide Roche with such API and finished Product [***].



**(b)** **Supplies for Activities After Option Exercise**. After Option exercise, Isis will deliver to Roche, if Roche desires, any inventory of cGMP API, non-GMP API, radiolabeled material, GMP and non-GMP finished Product, packaged clinical trial material, and non-GMP packaged trial material containing the Isis Development Candidate in Isis' possession [***].

**1.7.2.** **Supplies for Activities under the Brain Shuttle Development Candidate-R&D Plan**. The Parties will mutually agree on the quantity of API and research-grade Compound needed to support the Isis R&D Activities and Roche R&D Activities designated under the Brain Shuttle Development Candidate-R&D Plan. Roche will be responsible for all costs and expenses associated with supply of research-grade Compound, API and finished Product under the Brain Shuttle Development Candidate-R&D Plan.

**1.8.** **Requests to Work on an Additional Isis Development Candidate**.

**1.8.1.** ***Requests During the Option Period***.

**(a)** If, during the Option Period, Roche provides Isis a written request to discover and Develop a replacement or second Isis Development Candidate ("***Additional Isis Development Candidate***"), Isis will use Commercially Reasonable Efforts to perform such work under a mutually agreed amendment to the Isis Development Candidate-R&D Plan. The cost to perform such work leading up to the IND-Enabling Toxicology Studies will be paid by Roche in accordance with Section 1.8.3 below.

**(b)** If, during the Option Period, Roche provides Isis a written request to perform the IND-Enabling Toxicology Studies for the Additional Isis Development Candidate, Isis will use Commercially Reasonable Efforts to perform such work under a mutually agreed amendment to the Isis Development Candidate-R&D Plan. If the first Compound designated an Isis Development Candidate is being Developed under this Agreement when Isis receives such written request from Roche, then in lieu of Isis' actual costs to conduct the IND-Enabling Toxicology Studies on such Additional Isis Development Candidate, Roche shall pay Isis [***]. If, however, the first Compound designated an Isis Development Candidate has already completed IND-Enabling Toxicology Studies but is no longer being Developed under this Agreement when Isis receives such written request from Roche, then the [***] shall NOT be paid by Roche. Instead, Isis' [***] to conduct the IND-Enabling Toxicology Studies for the Additional Isis Development Candidate will be paid by Roche in accordance with Section 1.8.3 below.

**1.8.2.** ***Requests After Option Exercise***. If, after Option exercise, Roche provides Isis a written request to discover an Additional Isis Development Candidate, then Isis



will use Commercially Reasonable Efforts to discover an Additional Isis Development Candidate under a mutually agreed amendment to the Isis Development Candidate-R&D Plan, and once such Additional Isis Development Candidate is designated, Roche will be responsible for conducting the IND-Enabling Toxicology Studies for such Additional Isis Development Candidate. The cost to perform the work to discover an Additional Isis Development Candidate will be paid by Roche in accordance with Section 1.8.3 below. Roche's right to request Isis to perform the work described in this Section 1.8.2 expires [***], or if [***] but in no case later than [***] days after the [***].

**1.8.3.** ***Additional Isis Development Candidate-Cost Estimate - Payment Mechanics***. Before Isis starts any work requested under Section 1.8.1(a), Section 1.8.1(b) (if applicable), or Section 1.8.2, the Parties will finalize (via the JSC) a mutually agreed cost estimate covering Isis' estimate of its [***] by Isis in performing such work (including the cost of API and finished Product) (the "***Additional Isis Development Candidate-Cost Estimate***"). Before Isis commences any such work, Isis will provide the JSC with a good faith estimate of the cost for Isis to conduct and complete such work, and the JSC will discuss and unanimously agree on a final Additional Isis Development Candidate-Cost Estimate for Isis to conduct such activities. Isis will invoice Roche and Roche will pay Isis the Additional Isis Development Candidate-Cost Estimate using the same payment mechanism and schedule used under Section 1.6.1(b) and Section 1.6.1(c) above for Additional Costs.

**1.9.** **Subcontracting**. Each Party may engage Third Party subcontractors to perform certain of its obligations under this Agreement. Any subcontractor engaged to perform a Party's obligations under this Agreement will meet the qualifications typically required by such Party for the performance of work similar in scope and complexity and will execute such Party's standard nondisclosure agreement. Any Party engaging a subcontractor hereunder will remain responsible for such activities.

**1.10.** **Materials Transfer**. To facilitate the activities under an R&D Plan, either Party may provide certain materials for use by the other Party. All such materials will be used by the receiving Party in accordance with terms of this Agreement solely for purposes of exercising its rights and performing its obligations under this Agreement, and the receiving Party will not transfer such materials to any Third Party except with the written consent of the supplying Party. Except as expressly set forth herein, THE MATERIALS ARE PROVIDED "AS IS" AND WITHOUT ANY REPRESENTATION OR WARRANTY, EXPRESS OR IMPLIED, INCLUDING ANY IMPLIED WARRANTY OF MERCHANTABILITY OR OF FITNESS FOR ANY PARTICULAR PURPOSE OR ANY WARRANTY THAT THE USE OF THE MATERIALS WILL NOT INFRINGE OR VIOLATE ANY PATENT OR OTHER PROPRIETARY RIGHTS OF ANY THIRD PARTY.

**1.11.** **Applicable Laws**. Each Party will perform its activities pursuant to this Agreement in compliance with good laboratory and clinical practices and cGMP, in each case as

applicable under the laws and regulations of the country and the state and local government wherein such activities are conducted.

**1.12.** **Failure to Designate an Isis Development Candidate**. If, despite Isis' Commercially Reasonable Efforts, by the [***] anniversary of the Effective Date, Isis has not designated an Isis Development Candidate, then, notwithstanding any provision to the contrary in this Agreement (i) work under the Isis Development Candidate-R&D Plan will stop; (ii) the Parties' will no longer have an obligation to perform any activities under this ARTICLE 1 with respect to the Isis Development Candidate-R&D Plan; (iii) the Parties' respective obligations and Roche's rights under this Agreement with respect to the Isis Development Candidate-R&D Plan and any related Compounds will then terminate; (iv) Isis will have exclusive rights (and Roche will, and hereby does grant Isis an exclusive license) to all data, results and information generated under the Isis Development Candidate-R&D Plan, and Roche will promptly transfer to Isis copies of all such data, results and information in Roche's possession; and (v) Roche will and hereby does grant Isis an irrevocable, royalty-free, non-exclusive license to any Know-How and/or Patent Rights generated by Roche under the Isis Development Candidate-R&D Plan to research, develop, manufacture and commercialize ASOs designed to bind to the RNA encoding HTT. Isis will control any Jointly-Owned Collaboration Patents that resulted from the Isis Development Candidate-R&D Plan, and Roche will assign ownership to Isis on condition that Isis grants Roche an irrevocable, royalty-free, non-exclusive license for any purpose (other than researching, developing, manufacturing or commercializing products comprising an ASO).

**1.13.** **Failure to Designate a Brain Shuttle Development Candidate**. If, despite the Parties' Commercially Reasonable Efforts, by the [***] anniversary of the Effective Date, Roche has not designated a Brain Shuttle Development Candidate, then, notwithstanding any provision to the contrary in this Agreement (i) work under the Brain Shuttle Development Candidate-R&D Plan will stop; (ii) the Parties' will no longer have an obligation to perform any activities under this ARTICLE 1 with respect to the Brain Shuttle Development Candidate-R&D Plan; and (iii) the Parties' respective obligations and Roche's rights under this Agreement with respect to the Brain Shuttle Development Candidate-R&D Plan and any related Compounds will then terminate.



## ARTICLE 2.
## EXCLUSIVITY COVENANTS

**2.1.** **Exclusivity**.

**2.1.1.** **Exclusivity Covenants**. Each Party agrees that, except in the performance of its obligations or exercise of its rights under this Agreement, and except as set forth in Section 2.1.2 or Section 2.1.3:

**(a)** **The Parties' Exclusivity Covenants During the Option Period**. During the Option Period, each Party will work exclusively within the collaboration described in the Agreement to conduct all discovery, research, development, manufacture or commercialization of an ASO that is designed to bind to the RNA that encodes HTT in the Field.

**(b)** **The Parties' Exclusivity Covenants After Option Exercise**. After Option exercise:

**(i)** ***Developing an NAS Development Candidate***. If Roche is Developing or Commercializing a Development Candidate comprising a Non-Allele Selective Compound (an "***NAS Development Candidate***"), then until the Full Royalty Period ends in the first Major Market, neither Party nor any of its Affiliates or Sublicensees will sell an ASO approved by a Regulatory Authority for marketing and sale that is designed to bind to the RNA that encodes HTT in the Field. After the end of the Full Royalty Period in the first Major Market, the exclusivity covenants will continue on a country-by-country basis in each country where the Full Royalty Period still applies [***].

If, during the Reduced Royalty Period for such NAS Development Candidate, Isis (on its own or with a Third Party) following marketing approval sells an ASO designed to bind to the RNA that encodes HTT in the Field, then [***] and Roche's worldwide license under Section 4.1.1 solely with respect to such NAS Development Candidate will [***]; or

**(ii)** ***Developing an AS Development Candidate***. If (and for as long as) Roche is Developing or Commercializing a Development Candidate comprising an Allele Selective Compound (an "***AS Development Candidate***"), then through [***] prior to the anticipated end of the Full Royalty Period in the relevant country, neither Party nor any of its Affiliates or Sublicensees will file an NDA, MAA or JNDA, as applicable, for an ASO that is designed to bind to an SNP site within an HTT RNA associated with an expanded CAG repeat to selectively reduce the expanded CAG-repeat containing RNA relative to the normal HTT RNA (each



such ASO, an "***AS ASO***"); *provided*, *however*, that if within [***] for such AS Development Candidate but in no case later than [***], Roche does not request Isis to research and develop a second AS Development Candidate designed for use in a patient population substantially different from the patient population for the AS Development Candidate being developed or commercialized by Roche (as determined by genetic testing) (or if Roche later stops Developing or Commercializing such AS ASO), then, subject to the potential [***], Isis, its Affiliates or Sublicensees may sell AS ASOs designed for use in a patient population substantially different from the patient population for the AS Development Candidate being developed or commercialized by Roche (as determined by [***]) where [***] (Y) [***], or (Z) [***].

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

**(a)** Performance of the Isis R&D Activities;

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

**(c)** The granting of, or performance of obligations or exercise of rights under, Permitted Licenses.

**2.1.3.** **Limitations and Exceptions to Roche's Exclusivity Covenants**. Notwithstanding anything to the contrary in this Agreement, Roche's performance of the Roche R&D Activities will not violate Section 2.1.1.

**2.2.** **Effect of Exclusivity on Indications**. Isis and Roche are subject to certain exclusivity covenants under Section 2.1; *however*, the Parties acknowledge and agree that each Party (on its own or with a Third Party) may pursue products for any indication that are not designed to bind to the RNA that encodes HTT (or designed to selectively reduce HTT RNA alleles containing expanded CAG repeats), even if such products treat Huntington's Disease.

## ARTICLE 3.
## EXCLUSIVE OPTION

**3.1.** **Option and Option Deadline**. Isis hereby grants Roche an exclusive option to obtain the license set forth in Section 4.1.1 (the "***Option***"). To obtain the license set forth in Section 4.1.1, Roche must exercise the Option by the earlier of the following (the "***Option***



***Deadline***"): (i) the [***] following Roche's receipt of the Phase 1 Trial Data Package from Isis under Section 1.2.6 for the first Phase 1 Trial with an Isis Development Candidate (as such Phase 1 Trial is described in the Isis Development Candidate R&D Plan or as may otherwise be modified by the JSC); or (ii) [***] the Phase 1 Trial Data Package is available in the first Phase 1 Trial for a Brain Shuttle Development Candidate but in no case later than [***] after the last patient receives his/her last dose in such Phase 1 Trial; or (iii) [***].

**3.2.** **Option Exercise; Option Expiration**. If, by the Option Deadline, Roche (i) notifies Isis in writing that it is exercising the Option, and (ii) thereafter, Roche timely pays Isis the license fee set forth in Section 6.3, Isis will, and hereby does, grant Roche the license set forth in Section 4.1.1. Prior to the Option Deadline, Roche shall have the full opportunity to conduct due diligence to evaluate whether to exercise the Option and Isis shall cooperate with Roche and to ensure that all necessary data and information, including clinical and manufacturing data and any available [***] analysis, are provided to Roche. If, by the Option Deadline, Roche has not provided Isis a written notice stating that Roche is exercising its Option, and within thirty (30) days after providing such notice paid Isis the license fee set forth in Section 6.3, then Roche's Option will expire. If Roche's Option expires then Section 10.4.1 and Section 10.4.2 will apply.

**3.3.** **HSR**. If, by the Option Deadline, Roche notifies Isis in writing that it is exercising the Option, each Party shall (i) cooperate with the other Party in the preparation, execution and filing of all documents that may be required pursuant to the HSR Act or any other Applicable Law, and (ii) observe all applicable waiting periods before consummating the Option Exercise as set forth in Section 3.2. Each Party shall bear its own costs (including counsel or other expert fees) with respect to preparing, executing and filing such documents. Subject to the terms and conditions of this Agreement, each Party shall use all reasonable efforts to take, or cause to be taken, all reasonable actions and to do, or cause to be done, all things necessary and appropriate to consummate the exercise of the Option contemplated by Section 3.2 of this Agreement, should Roche choose to exercise the Option. Notwithstanding anything to the contrary contained in this Agreement, Roche shall have the sole and exclusive right to determine, at its discretion but without any obligation whatsoever, whether it shall have any obligation to take any actions in connection with, or agree to, any demands for the license, sale, divestiture or disposition of assets of Roche or its Affiliates or Isis, asserted by the United States Federal Trade Commission, the Antitrust Division of the United States Department of Justice or any other Regulatory Authority in connection with antitrust matters or international competition laws, or to defend through litigation any proceeding commenced by the Federal Trade Commission, the Antitrust Division of the United States Department of Justice or other Governmental Authority in connection with the foregoing matters.



## ARTICLE 4.
## LICENSE GRANTS

**4.1.** **License Grants; Sublicense Rights**.

**4.1.1.** **Development and Commercialization License Grant to Roche**. Subject to the terms of this Agreement, effective upon Roche's exercise of the Option in accordance with this Agreement, Isis grants to Roche a worldwide, exclusive, royalty-bearing, sublicensable (in accordance with Section 4.1.4 below) license under the Licensed Technology to research, Develop, Manufacture, have Manufactured (in accordance with Section 4.1.4 below) and Commercialize Products in the Field.

**4.1.2.** **Brain Shuttle IP Licenses**. As further specified in Section 7.1.3, the Joint Patent Committee will classify the Brain Shuttle Collaboration Patents into the following sub-categories: (w) Brain Shuttle-Specific Collaboration Patents, (x) ASO-Specific Collaboration Patents, (y) Linker-Specific Collaboration Patents, and (z) Omnibus Collaboration Patents. With respect to each such sub-category of Brain Shuttle Collaboration Patents, the Parties grant one another the following licenses:

**(a)** ***Licenses to Roche to Brain Shuttle Collaboration Patents***. Subject to the terms of this Agreement, Isis hereby grants to Roche:

**(i)** a worldwide, exclusive, sublicensable license under any Brain Shuttle-Specific Collaboration Patents, Linker-Specific Collaboration Patents and Omnibus Collaboration Patents solely or jointly-owned by Isis or its Affiliates, to research, develop, manufacture, have manufactured and commercialize products comprising an active pharmaceutical ingredient and the Brain Shuttle Technology (each such product, a "***BS-Specific Drug***"); and

**(ii)** a worldwide, non-exclusive, sublicensable license under any Linker-Specific Collaboration Patents and Omnibus Collaboration Patents solely or jointly-owned by Isis or its Affiliates, to research, develop, manufacture, have manufactured and commercialize products.

**(b)** ***Licenses to Isis to Brain Shuttle Collaboration Patents***. Subject to the terms of this Agreement (including Isis' exclusivity covenants under Section 2.1.1), Roche hereby grants to Isis:

**(i)** a worldwide, exclusive, sublicensable license under any ASO-Specific Collaboration Patents, Linker-Specific Collaboration Patents and Omnibus Collaboration Patents solely or jointly-owned by Roche or its Affiliates, to research, develop, manufacture, have manufactured and commercialize products that include an ASO as an active pharmaceutical ingredient and are not BS-Specific Drugs; and



**(ii)** a worldwide, non-exclusive, sublicensable license under any Linker-Specific Collaboration Patents and Omnibus Collaboration Patents solely or jointly-owned by Roche or its Affiliates, to research, develop, manufacture, have manufactured and commercialize products.

**4.1.3.** **Amendment to the Existing Diagnostic Agreement**. After Option exercise, Isis and Roche will execute an amendment to the Existing Diagnostic Agreement on terms mutually agreed by Roche and Isis, which amendment will include granting Roche a non-exclusive, sublicensable, worldwide license, with the right to sublicense (through multiple tiers) under Patent Rights and/or Know-How Controlled by Isis necessary or useful to develop and commercialize HTT diagnostic products (including diagnostic products and/or services to select patients who will use Products).

**4.1.4.** **Sublicense Rights**.

**(a)** Subject to the terms of this Agreement, Roche will have the right to grant sublicenses under any license granted under Section 4.1.1 above:

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

**(ii)** under the Isis Manufacturing and Analytical Patents and Isis Manufacturing and Analytical Know-How solely to (y) an Affiliate of Roche or (z) [***] (each, a "***Licensed CMO***").

**(b)** **Requests to Grant Sublicenses to CMOs**. If Roche provides Isis with a written request that Isis grant a license under the Isis Manufacturing and Analytical Patents and Isis Manufacturing and Analytical Know-How to a CMO designated by Roche that is not a Licensed CMO, solely for such CMO to manufacture Products for Roche, its Affiliate or Sublicensee in a manufacturing facility owned or operated by such CMO, [***].

**(c)** **Enforcing Sublicenses**. Each sublicense by Roche under this Agreement will be subject to, and consistent with, the terms of this Agreement. Roche shall be responsible to ensure compliance by its Sublicensees with the terms and conditions of this Agreement. If Isis reasonably believes a Roche Sublicensee may be violating the terms of this Agreement, then, within 30 days after Isis delivers a written request to Roche, Roche will provide Isis a full and complete copy of the sublicense Roche entered with such Sublicensee.



**(d)** **Effect of Termination on Sublicenses**. If this Agreement terminates for any reason, any Sublicensee granted a sublicense by Roche to Develop or Commercialize Products will, from the effective date of such termination, automatically become a direct licensee of Isis with respect to the rights sublicensed to the Sublicensee by Roche; *so long as* (i) such Sublicensee is not in breach of its sublicense agreement, (ii) such Sublicensee agrees in writing to comply with all of the terms of this Agreement to the extent applicable to the rights originally sublicensed to it by Roche, and (iii) such Sublicensee agrees to pay directly to Isis such Sublicensee's payments under this Agreement to the extent applicable to the rights sublicensed to it by Roche. Roche agrees that it will confirm clause (i) of the foregoing in writing at the request and for the benefit of Isis and if requested, the Sublicensee.

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

**4.1.6.** **License Conditions; Limitations**. Subject to Section 6.11, any license granted under Section 4.1.1 and the sublicense rights under Section 4.1.4 are subject to and limited by (i) the Permitted Licenses, (ii) the Prior Agreements, and (iii) the Isis In-License Agreements, in each case to the extent the provisions of such obligations or agreements are specifically disclosed to Roche in writing (or via electronic data room).

**4.1.7.** **Trademarks for Products**. After Option exercise, Roche is solely responsible for all trademarks, trade dress, logos, slogans, designs, copyrights and domain names used on or in connection with Products licensed under Section 4.1.1.

**4.2.** **Technology Transfer after Option Exercise**. After Option exercise pursuant to a technology transfer plan to be mutually agreed by Isis and Roche, and subject to Section 4.2.3, Isis will:

**4.2.1.** **Licensed Know-How — Generally**. Deliver to Roche copies of Licensed Know-How (other than the Isis Manufacturing and Analytical Know-How) in the Field in Isis' possession not previously provided hereunder, for use solely in accordance with the license granted under Section 4.1.1 to Roche together with all regulatory documentation (including drafts) related to Products. To assist with the transfer of such Licensed Know-How, Isis will make its personnel reasonably available to Roche during normal business hours to transfer such Licensed Know-How under this Section 4.2.1.



**4.2.2.** **Isis Manufacturing and Analytical Know-How**. Deliver, at Roche's election, to one of either (i) Roche, or (ii) a Licensed CMO solely to Manufacture API on Roche's behalf, copies of the Isis Manufacturing and Analytical Know-How relating to Products in Isis' possession not previously provided hereunder, which is necessary for the exercise by Roche, its Affiliates or a Third Party of the Manufacturing rights granted under Section 4.1.1.

**4.2.3.** **Technology Transfer Costs**. Isis will perform the technology transfer activities under this Section 4.2 for up to [***] FTE hours (free of charge to Roche) of Isis' time. Thereafter, if requested by Roche, Isis will provide Roche with a reasonable level of assistance in connection with such transfer, which Roche will reimburse Isis for Isis' time incurred in providing such assistance at Isis' FTE rate, and any of Isis' reasonable travel expenses for travel requested by Roche, and any outside consultants' costs and consultants' reasonable travel expenses incurred by Isis agreed in advance by Roche.

## ARTICLE 5.

## DEVELOPMENT, MANUFACTURING AND COMMERCIALIZATION

**5.1.** **Roche Diligence**. After Option exercise, subject to the terms of this Agreement, Roche is solely responsible for all Development, Manufacturing and Commercialization activities, and for all costs and expenses associated therewith, with respect to the Development, Manufacture and Commercialization of Products. Roche will use Commercially Reasonable Efforts to Develop, Manufacture and Commercialize Products, including to meet the timelines and milestones set forth in the Isis Development Candidate-R&D Plan, the IDCP and the Specific Performance Milestone Events.

Prior to Initiation of the first Registration-Directed Trial for a given Product, Roche will prepare a Development and global integrated development and commercialization plan ("***IDCP***") outlining key aspects for Developing such Product through Approval, and Roche's worldwide strategy to launch and Commercialize such Product. The IDCP will incorporate and replace the applicable R&D Plan and will take the form of, and contain information consistent with, Roche's Development and Commercialization plans for its similar products at similar stages of development or commercialization, including Product Sales forecasts. Once Roche has prepared such plan, Roche will update the IDCP consistent with Roche's standard practice and provide such updates to Isis at least Annually.

**5.1.1.** **Independent Expert**. After Option exercise, Roche will have the final decision-making authority regarding which Product to [***], and Roche will present its decision to the JSC. If Roche decides to progress the [***], and the JSC does not unanimously agree with Roche's decision to do so, the JSC will appoint a single, independent Third Party expert ("***Independent Expert***") mutually agreed upon by



the Parties with appropriate expertise and professional credentials to evaluate Roche's decision. Each Party will have the opportunity to present its position to the Independent Expert. The Independent Expert, when considering its recommendation, will consider such factors as [***], available clinical and pre-clinical data for [***], the commercial potential of the Development Candidates and the competitive environment. The Independent Expert will make his or her own recommendation to the JSC regarding whether the Brain Shuttle Development Candidate or the Isis Development Candidate should [***]. Roche will not be required to adopt the Independent Expert's recommendation. If the Independent Expert recommends that the [***], [***], then Roche will pay Isis the royalty rate under TABLE 4 of Section 6.7.1 applicable to [***]. If the Independent Expert recommends that the [***], Roche will pay the costs of the Independent Expert. If the Independent Expert recommends that the [***], Roche and Isis will each pay 50% of the costs of the Independent Expert.

**5.1.2.** **Phase 2 Trials**. The Phase 2 Trial for the first Isis Development Candidate will be designed in accordance with the Phase 2 Trial design set forth in the Isis Development Candidate-R&D Plan, taking into consideration the results of the Phase 1 Trial. The Phase 2 Trials for all other Development Candidates will be designed in accordance with the applicable R&D Plan. Roche will keep Isis informed of the progress and status of each Phase 2 Trial. Roche will notify Isis in writing promptly after Roche completes a Phase 2 Trial under the applicable R&D Plan. Promptly after such notice, once the data generated under the statistical analysis plan for a Phase 2 Trial is available to Roche, Roche will provide such data to Isis.

**5.1.3.** **Registration-Directed Trials**. The Registration-Directed Trials will be designed in accordance with the Registration-Directed Trial designs set forth in the applicable IDCP. Roche will keep Isis informed of the progress and status of each Registration-Directed Trial. Roche will notify Isis in writing promptly after Roche completes each Registration-Directed Trial under the applicable IDCP. Promptly after such notice, once the data generated under the statistical analysis plan for a Registration-Directed Trial is available to Roche, Roche will provide such data to Isis.

**5.1.4.** **Investigator's Brochure**. After Option Exercise, in addition to the IDCP, Roche will keep Isis reasonably informed with respect to the status, activities and progress of Development of Products by providing updated versions of the Investigator's Brochure to Isis Annually and upon any substantive change to the safety or risk of the Products.

**5.1.5.** **Participation in Regulatory Meetings**. Each Party will provide the other Party with as much advance written notice as practicable of any meetings such Party has or plans to have with a Regulatory Authority regarding pre-approval or Approval matters for a Product, and will allow the other Party (at such other Party's own expense) to participate in any such meetings as an observer.

**5.1.6.** **Regulatory Communications**. Each Party will provide the other Party with copies of documents and communications submitted to and received from Regulatory Authorities that materially impact the Development or Commercialization of Products for the other Party's review and comment, and the submitting Party will consider in good faith including any comments provided by the reviewing Party to such documents and communications.

**5.1.7.** **Participation in Roche Clinical Development Team Meetings**. [***], Roche will permit Isis to participate in Roche's key clinical development team meetings for Products (i.e., meetings that are likely to have a material impact on the Development of the Product(s)) (each such meeting, a "***Key Meeting***"), at Isis' reasonable request. Isis' and Roche's respective designated clinical leaders will work together to come up with a schedule of such Key Meetings, giving Isis as much advance written notice as practicable so that Isis may, at Isis' expense, plan for its participation in such meetings.

**5.1.8.** **Class Generic Claims**. If Roche intends to make any claims in a Product label or regulatory filing that are class generic to ASOs or Isis' chemistry platform(s), Roche will provide such claims and regulatory filings to Isis in advance and will consider in good faith any proposals and comments made by Isis.

**5.1.9.** **Applicable Laws**. Roche will perform its activities pursuant to this Agreement in compliance with applicable good laboratory and clinical practices and cGMP.

**5.2.** **IND; Global Safety Database.**

**5.2.1.** **IND**. The Parties acknowledge that until the first Development Candidate completes a Phase 1 Trial, Isis will be the holder of the IND for such Development Candidate. After Option exercise, upon transfer of Isis' Development Candidate IND to Roche and assumption by Roche of regulatory responsibilities under the IND, Roche will assume responsibility for the global safety database related to such Development Candidate. After Option exercise, Roche will be solely responsible for reporting to Regulatory Authorities in accordance with the Applicable Law for expeditable adverse events and for periodic safety reporting relating to the safety of such Development Candidate and all subsequent Development Candidates and will furnish copies of such reports to Isis.

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

**(a)** Isis maintains an internal database that includes information regarding the tolerability of its drug compounds, individually and as a class, including information discovered during pre-clinical and clinical development (the "***Isis Internal ASO Safety Database***"). In an effort to maximize understanding of the safety profile and pharmacokinetics of Isis compounds, after Option exercise, Roche will cooperate in connection with populating the Isis Internal ASO Safety Database. To



the extent collected by Roche and in the form in which Roche uses/stores such information for its own purposes, Roche will make available to Isis information concerning toxicology, pharmacokinetics, safety pharmacology study(ies), serious adverse events and other safety information related to Products as soon as practicable following the date such information is available to Roche (but Roche will make such information available to Isis starting no later than thirty (30) days after Roche's receipt of such information). In connection with any reported serious adverse event, Roche will provide Isis all serious adverse event reports, including initial, interim, follow-up, amended, and final reports. In addition, with respect to Products, Roche will make available to Isis copies of Annual safety updates filed with each IND and the safety sections of any final Clinical Study reports within thirty (30) days following the date such information is filed or is available to Roche, as applicable. Furthermore, Roche will promptly make available to Isis any supporting data and answer any follow-up questions reasonably requested by Isis. All such information disclosed by Roche to Isis will be Roche Confidential Information; *provided*, *however*, that Isis may disclose any such Roche Confidential Information to (i) Isis' other partners pursuant to Section 5.2.2(b) below if such information is regarding class generic properties of ASOs, or (ii) any Third Party, in each case, so long as Isis does not disclose the identity of a Product or Roche. Roche will contact Isis' Chief Medical Officer at Isis Pharmaceuticals, Inc., 2855 Gazelle Court, Carlsbad, California 92010 (or at such other address/contact designated in writing by Isis) for matters related to the Isis Internal ASO Safety Database. Roche will also cause its Affiliates and Sublicensees to comply with this Section 5.2.2(a).

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

## ARTICLE 6.
## FINANCIAL PROVISIONS

**6.1.** **Option Fee**. In partial consideration for Roche's Option hereunder, within ten (10) days following the Effective Date and receipt by Roche of an invoice from Isis, Roche will pay Isis an Option fee equal to thirty million dollars (US$30,000,000).



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

achieved by the applicable Development Candidate:

**TABLE 1**

| Pre-Licensing Milestone Events | Column 1 Milestone Payments for the Isis Development Candidate to First Achieve Milestone Event | Column 2 Milestone Payments for Additional Isis Development Candidate to Achieve Milestone Event | Column 3 Milestone Payments for First Brain Shuttle Development Candidate to Achieve Milestone Event |
|---|---|---|---|
| [***] | [***] | [***] | [***] |
| [***] | [***] | [***] | [***] |

*[***] milestone payment is only payable once in accordance with Section 1.8.1(b).

†This milestone payment is not payable by Roche if Roche has already paid Isis the [***] milestone payment under Column 1 of this TABLE 1.

Except for the [***] milestone payment in Column 2 of TABLE 1 for an Additional Isis Development Candidate, Roche will pay to Isis the Milestone Event payments as set forth in TABLE 1 after the applicable Milestone Event is first achieved by a Development Candidate even if Roche has exercised the Option prior to achievement of the Milestone Event.

**6.3.** **License Fee**. Pursuant to Section 3.2, subsequent to Roche's written notice to exercise its Option in accordance with this Agreement, Roche will pay to Isis a license fee of [***] within thirty (30) days after providing such written notice and receipt by Roche of an invoice from Isis.

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



**TABLE 2**

| Post-Licensing Milestone Event | Column 1 Milestone Payment for First Product to Achieve Milestone Event | Column 2 Milestone Payment for Each Product After the First Product to Achieve Milestone Event |
|---|---|---|
| [***] | [***] | [***] |
| [***] | [***] | [***] |
| [***] | [***] | [***] |
| [***] | [***] | [***] |
| [***] | [***] | [***] |
| [***] | [***] | [***] |
| [***] | [***] | [***] |
| [***] | [***] | [***] |
| [***] | [***] | [***] |

**6.5.** **Milestone Payments for First Achievement of Sales Milestone Event**. Roche will pay Isis the applicable one-time milestone payments set forth in TABLE 3 below after the first achievement of the listed events, by or on behalf of Roche or its Affiliates or Sublicensees. For clarity, notwithstanding any provision to the contrary in this Agreement, any consideration received by Roche or its Affiliates from a Compulsory Sublicensee for the sale of Products in a given Calendar Year will be added to Net Sales of Products for such year for purposes of determining whether any of the Sales Milestones in TABLE 3 have been achieved.

**TABLE 3**

| Sales Milestone | Sales Milestone Payment |
|---|---|
| [***] in aggregate worldwide Annual Net Sales of Products comprising an Isis Development Candidate | [***] |
| [***] in aggregate worldwide Annual Net Sales of Products comprising an Isis Development Candidate | [***] |
| [***] in aggregate worldwide Annual Net Sales of Products comprising a Brain Shuttle Development Candidate | [***] |
| [***] in aggregate worldwide Annual Net Sales of Products comprising a Brain Shuttle Development Candidate | [***] |
| **Total Sales Milestone Payments** | [***] |



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

**6.6.1.** Each milestone payment set forth in TABLE 1, and in Column 1 of TABLE 2 above, will be paid only once upon the first achievement of the Milestone Event regardless of how many times such Milestone Event is achieved. On a Product-by-Product basis, each milestone payment set forth in Column 2 of TABLE 2 above will be paid only once upon the first achievement of the Milestone Event by the

applicable Product. Each milestone payment set forth in TABLE 3 above will be paid only once upon the first achievement of the Milestone Event.

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

**6.6.3.** Each time a Milestone Event is achieved under this ARTICLE 6, the Party that achieved such Milestone Event will send to the other Party a written notice thereof promptly (but no later than ten (10) Business Days) following the date of achievement of such Milestone Event and such payment will be due within thirty (30) days of the date such Milestone Event was achieved and receipt of an invoice by Roche from Isis.

**6.7. Royalty Payments to Isis**.

**6.7.1.** **Roche Full Royalty**. As partial consideration for the rights granted to Roche hereunder, subject to the provisions of this Section 6.7.1 and Section 6.7.2, Roche will pay to Isis royalties on Annual worldwide Net Sales of Products sold by Roche, its Affiliates or Sublicensees, on a country-by-country and Product-by-Product basis, in each case in the amounts as follows in TABLE 4 below (the "***Roche Full Royalty***"):



**TABLE 4**

| Royalty Tier | Annual Worldwide Net Sales | Royalty Rate for Products Comprising: Isis Development Candidate | Brain Shuttle Development Candidate | Roche-Selected Brain Shuttle Development Candidate |
|---|---|---|---|---|
| 1 | For the portion of Annual Worldwide Net Sales < $[***] | [***]% | [***]% | [***]% |
| 2 | For the portion of Annual Worldwide Net Sales > $[***] but < $[***] | [***]% | [***]% | [***]% |
| 3 | For the portion of Annual Worldwide Net Sales > $[***] but < $[***] | [***]% | [***]% | [***]% |
| 4 | For the portion of Annual Worldwide Net Sales > $[***] | [***]% | [***]% | [***]% |

**(a)** Annual worldwide Net Sales for a particular Product will be calculated by [***]. For clarity, notwithstanding any provision to the contrary in this Agreement, any consideration received by Roche or its Affiliates from a Compulsory Sublicensee solely for the sale of Products in a given Calendar Year will be added to Net Sales of Products for such year for purposes of determining which royalty tier (and therefore which royalty rate) applies to a particular Product in TABLE 4.

**(b)** Roche will pay Isis royalties on Net Sales of Products arising from named patient and other similar programs under Applicable Laws, and Roche will provide reports and payments to Isis consistent with Section 6.12. No royalties are due on Net Sales of Products arising from compassionate use and other programs providing for the delivery of Product at no cost. The sales of Products arising from named patient, compassionate use or other similar programs will not be considered a First Commercial Sale for purposes of determining the Full Royalty Period.

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

**(a)** **Full Royalty Period**. Roche's obligation to pay Isis the Roche Full Royalty above with respect to a Product will continue on a country-by-country and Product-by-Product basis from the date of First Commercial Sale of such Product until the later of the date of expiration of (i) the last Valid Claim within the Licensed Patents or the Brain Shuttle Collaboration Patents Covering such Product in the country in which such



Product is used or sold, (ii) the data exclusivity period conferred by the applicable Regulatory Authority in such country with respect to such Product (e.g., such as in the case of an orphan drug), or (iii) the [***] anniversary of the First Commercial Sale of such Product in such country; *provided, however*, that, on a country-by-country and Product-by-Product basis, if neither of the periods set forth in clause (i) and clause (ii) of this Section 6.7.2(a) apply to a Product, then the Roche Full Royalty will continue to apply through the [***] anniversary of the First Commercial Sale of such Product in such country *unless* a [***] in such country, at which time in lieu of paying the Roche Full Royalty, Roche will pay Isis the Roche Reduced Royalty for such Product in such country in accordance with Section 6.7.2(b) (such royalty period, the "***Full Royalty Period***"). For clarity, (X) Licensed Patents that are jointly-owned by Roche, and (Y) Brain Shuttle Collaboration Patents that are jointly or solely-owned by Roche or its Affiliates, will count toward the calculation of the Full Royalty Period in a particular country if the use or sale of a Product by an unauthorized Third Party in such country would infringe a Valid Claim of such Licensed Patent or Brain Shuttle Collaboration Patent.

**(b)** **Reduced Royalty Period**. Subject to Section 6.7.2(c), on a country-by-country and Product-by-Product basis, after the expiration of the Full Royalty Period in a country and until the end of the Reduced Royalty Period, in lieu of the royalty rates set forth in

TABLE 4 of Section 6.7.1, Roche will pay Isis royalty rates (the "***Roche Reduced Royalty***") on Net Sales of Products in such country calculated on a Calendar Quarter-by-Calendar Quarter basis by [***]; *provided, however*, that the Roche Reduced Royalty rate in each country will in no event exceed the Reference Rate applicable under this Section 6.7. For example, if peak Calendar Year Net Sales of a Product comprising an Isis Development Candidate during the Full Royalty Period were [***] and royalties paid for that same Calendar Year were [***] resulting in a [***], and if [***] and the [***], the applicable [***] in such country would be [***]. Similarly, if the quarterly [***], then the applicable [***] in such country would be [***].

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

**(i)** In no event will the aggregate royalty reductions under Section 6.7.2(b) and/or Section 6.8 reduce the royalties payable to Isis on Net Sales of a Product in any given period to an amount that is less than the [***].

**(ii)** In no event will the aggregate royalty offsets under Section 6.11.3(b) reduce the royalties payable to Isis on Net Sales of a Product in any given period to an amount that is less than the greater of (i) [***], and (ii) [***].



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

**(e)** **Royalty Examples**. SCHEDULE 6.7.2(e) attached hereto contains examples of how royalties will be calculated under this Section 6.7.

**(f)** **Allocation of Net Sales**. If, by reason of one or more royalty rate adjustments under this Section 6.7.2, different royalty rates apply to Net Sales of Products from different countries, Roche will [***] such Net Sales [***]. SCHEDULE 6.7.2(f) attached hereto contains examples of how Net Sales of Products from different countries at different royalty rates will be [***].

**6.8.** **Royalty Reduction Due to Decline In Product Sales Clearly Attributable to Sales of an [***]**. If, after taking into account the then available data, including but not limited to epidemiology data, any Third Party product sales and diagnostics sales data and relevant market research information, Roche determines (and provides written notice to Isis of such determination and the basis therefor) that any decline in sales of the AS Development Candidate being Commercialized by Roche is clearly attributable to the sales of any [***], then, subject to Section 6.7.2(c)(i), the royalty rates under TABLE 4 applicable to such AS Development Candidate being Commercialized by Roche, its Affiliates or Sublicensees [***]. For example, if Roche determines such decline in sales to be [***], then Roche shall reduce royalties otherwise payable to Isis based on the actual Net Sales for that Calendar Quarter [***]. If Roche implements a royalty reduction under this Section 6.8, Roche will make such reductions with a one Calendar Quarter delay in order to generate the data and supporting calculations necessary to determine the amount of any such reduction, and Roche shall include its calculation of such reduction in the applicable royalty report under Section 6.12.2. If Isis believes that any decline in sales of the AS Development Candidate being Commercialized by Roche is not clearly attributable to the sales of any such [***], the Parties will discuss the matter in good faith and if the Parties cannot resolve such matter it will be resolved in accordance with the dispute resolution process set forth in Section 12.1. Roche is not entitled to any royalty reduction under this Section 6.8 as a result of sales of [***].

**6.9.** **Apportionment of Compulsory Sublicensee Consideration**. At such time as Roche or any of its Affiliates or Sublicensees enters into a sublicense with a Compulsory Sublicensee, the Parties will discuss and mutually agree upon an adjustment of the royalty due to Isis under Section 6.7 of this Agreement with respect to sales of Products by such Compulsory Sublicensee, with such adjustment calculated based on a [***].



**6.10.** **Reverse Royalty Payments to Roche for Discontinued Products**.

**6.10.1.** **Reverse Royalty for a Discontinued Product Comprising an Isis Development Candidate**. If Isis or any of its Affiliates or Sublicensees Commercializes a Discontinued Product for which Roche has paid Isis the license fee under Section 6.3 and such Discontinued Product (i) is comprised of an Isis Development Candidate, and (ii) was not commercialized by Roche, its Affiliates or its Sublicensees, then following the First Commercial Sale of such Discontinued Product by Isis or its Affiliates or Sublicensees, Isis will pay Roche a royalty of [***] of Annual worldwide net sales of such Discontinued Product ("***Isis Development Candidate Reverse Royalties***"). Isis will pay Roche such Isis Development Candidate Reverse Royalties in accordance with the provisions governing payment of royalties from Roche to Isis in Sections 6.7.2, 6.11, 6.12, 6.13, 6.14, and 6.15 (*mutatis mutandis*); *provided, however*, that Isis' obligation to pay Roche Isis Development Candidate Reverse Royalties will expire once Isis has paid Roche an amount equal to [***] for such Discontinued Product under Section 6.2 and Section 6.4.

**6.10.2.** **Reverse Royalty for a Discontinued Product Comprising a Brain Shuttle Development Candidate**. If Roche has paid Isis the license fee under Section 6.3 and Isis or any of its Affiliates or Sublicensees Commercializes a Discontinued Product that is comprised of a Brain Shuttle Development Candidate, then following the First Commercial Sale of such Discontinued Product by Isis or its Affiliates or Sublicensees, Isis will pay Roche a royalty of [***] of Annual worldwide net sales of such Discontinued Product ("***Brain Shuttle Development Candidate Reverse Royalties***"). Isis will pay Roche Brain Shuttle Development Candidate Reverse Royalties in accordance with (and for the same duration as) the provisions governing payment of royalties from Roche to Isis in Sections 6.7.2, 6.11, 6.12, 6.13, 6.14, and 6.15, *mutatis mutandis*.

**6.11.** **Third Party Payment Obligations**.

**6.11.1.** **Existing In-License Agreements**.

**(a)** ***Isis' Existing In-License Agreements***. Certain of the Licensed Technology Controlled by Isis as of the Effective Date licensed to Roche under Section 4.1.1 are in-licensed or were acquired by Isis under the agreements with Third Party licensors or sellers listed on SCHEDULE 6.11.1 (such license or purchase agreements being the "***Isis In-License Agreements***"), and certain milestone or royalty payments and license maintenance fees may become payable by Isis to such Third Parties under the Isis In-License Agreements based on the Development or Commercialization of a Product by Roche under this Agreement. Any payment obligations arising under the Isis In-License Agreements as they apply to Products that:

**(i)** accrue prior to Option exercise, will be paid by [***] as [***]; and



**(ii)** accrue after Option exercise, will be paid by [***] as [***].

**(b)** ***Isis' Agreements at the time of Option Exercise.*** Prior to Roche exercising the Option, Isis shall disclose to Roche all agreements (other than the In-License Agreements) entered into after the Effective Date by Isis with Third Party licensors or sellers under which Isis licensed or acquired any Licensed Technology to be licensed to Roche under Section 4.1.1 ("***Additional Isis In-License Agreements***"). Any payment obligations arising under any Additional Isis In-License Agreements as they apply to Products that:

**(i)** accrue prior to Option exercise, will be paid by [***] as [***]; and

**(ii)** accrue after Option exercise, will be paid by [***] as [***], in which case Section 6.11.3 will apply.

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

**6.11.2. New In-Licensed Product-Specific Patents**.

**(a)** On a Product-by-Product basis, after Option exercise, Roche or Isis, as the case may be, will promptly provide the other Party written notice of any additional Third Party Patent Rights it has identified as necessary to Develop or Commercialize a Product where such Third Party Patent Rights would be considered a Product-Specific Patent if either Party Controlled such Patent Rights ("***Additional Product-Specific Patents***"), and Roche will have the first right, but not the obligation, to negotiate with, and obtain a license from the Third Party Controlling such Additional Product-Specific Patents. If Roche obtains any such Additional Product-Specific Patents then any financial obligations under such Third Party agreement will be paid solely by [***] as [***].

**(b)** If, however, Roche elects not to obtain such a license to such Additional Product-Specific Patents, Roche will so notify Isis, and Isis may obtain such a license to such Additional Product-Specific Patents and Isis will include such Additional Product-Specific Patents in the license granted to Roche under Section 4.1.1 provided that Roche agrees in writing to [***].



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

**(a)** Roche will promptly provide Isis written notice of any [***] ("***Additional Core IP***") that Roche believes it has identified and Isis will have the first right, but not the obligation, to negotiate with, and obtain a license from the Third Party Controlling such Additional Core IP. For clarity, Additional Core IP does not include any Patent Rights claiming (or intellectual property related to) [***]. If Isis obtains such a Third Party license, Isis will include such Additional Core IP in the license granted to Roche under Section 4.1.1, and any financial obligations under such Third Party agreement will be paid solely by [***] as [***].

**(b)** If, however, Isis elects not to obtain such a license to such Third Party intellectual property, Isis will so notify Roche, and Roche may obtain such a Third Party license and, subject to Section 6.7.2(c)(ii), Roche may offset an amount equal to [***] of [***] paid by Roche under such Third Party license against any [***] of this Agreement in such country for [***].

**(c)** If Isis does not agree with Roche that a license to such Third Party Patent Rights is necessary to [***], then Isis will send written notice to such effect to Roche, and the Parties will engage a mutually agreed independent Third Party intellectual property lawyer with expertise in the patenting of ASOs, and appropriate professional credentials in the relevant jurisdiction, to determine the question of whether or not such Third Party intellectual property is Additional Core IP. The determination of the Third Party expert engaged under the preceding sentence will be binding on the Parties solely for purposes of determining whether Roche is permitted to [***]. The costs of any Third Party expert engaged under this Section 6.11.3(c) will be paid by the Party against whose position the Third Party lawyer's determination is made.

**6.12. Payments**.

**6.12.1. Commencement**. Beginning with the Calendar Quarter in which the First Commercial Sale, named patient sale, compassionate use sale or other similar sales for a Product is made and for each Calendar Quarter thereafter, Roche will make royalty payments to Isis under this Agreement within [***] following the end of each such Calendar Quarter.

**6.12.2. Royalty Reporting**. Each royalty payment will be accompanied by a report, summarizing in writing for the relevant Calendar Quarter on a Product-by-Product basis the following information:

**(a)** Sales in Swiss Francs on a country-by-country basis;

**(b)** Net Sales in Swiss Francs on a country-by-country basis;



**(c)** Total worldwide Net Sales in Swiss Francs;

**(d)** Exchange rate used for the conversion of Net Sales from Swiss Francs to US Dollars pursuant to Section 6.12.4;

**(e)** Royalty Rate pursuant to Section 2.1.1(b)(ii) (if applicable), Section 6.7.1 and Section 6.7.2, as applicable; and

**(f)** Total Royalty payable in US Dollars.

In addition, Roche will include in each report under this Section 6.12.2 information regarding any Net Sales of Products sold for named patient, compassionate use or other similar sales and any consideration received from any Compulsory Sublicensees.

**6.12.3.** After first Approval, if no royalties or other payments from Product sales are payable in respect of a given Calendar Quarter, Roche will submit a written royalty report to Isis so indicating together with an explanation as to why no such royalties are payable. In addition, beginning with the Calendar Quarter in which the First Commercial Sale for a Product (or any named patient sale, compassionate use sale or other similar sales of a Product) is made and for each Calendar Quarter thereafter, within ten (10) Business Days following the end of each such Calendar Quarter, Roche will provide Isis a [***] report estimating the total (A) Sales and Net Sales for Products projected for such Calendar Quarter, and (B) if available, the amount of any consideration payable to Roche under sublicenses with Compulsory Sublicensees.

**6.12.4.** **Mode of Payment**. All payments under this Agreement will be (i) payable in full in U.S. Dollars, regardless of the country(ies) in which sales are made, (ii) made by wire transfer of immediately available funds to an account designated by Isis in writing, and (iii) irrevocable and non-refundable. Any corrections to calculations of royalty payments previously paid shall be adjusted to the next royalty payment due. When calculating the Sales of a Product that occur in currencies other than U.S. Dollars, Roche will convert the amount of such sales into Swiss Francs and then into U.S. Dollars using Roche's then current internal foreign currency translation actually used on a consistent basis in preparing its audited financial statements (currently YTD average rate as reported by Reuters).

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

**6.13.** **Audits**. After the first Approval of a Product, during the remaining Agreement Term and for a period of thirty-six (36) calendar months thereafter, at the request and expense of Isis, Roche will permit an independent certified public accountant of internationally recognized standing appointed by Isis, at reasonable times and upon at least sixty (60)



Business Days written notice, but in no case more than once per Calendar Year, to examine such records as may be necessary for the purpose of verifying the calculation and reporting of Net Sales and the correctness of any royalty payment made under this Agreement for any period within the preceding thirty-six (36) calendar months. No Calendar Year can be audited more than once. Any and all records of Roche examined by such independent certified public accountant will be deemed Roche's Confidential Information. The independent certified public accountant shall share all draft reports with Roche before the draft audit report is shared with Isis and before the final document is issued. Upon completion of the audit, the accounting firm will provide both Roche and Isis with a written report disclosing whether the royalty payments made by Roche are correct and the specific details concerning any discrepancies ("***Audit Report***"). If, as a result of any inspection of the books and records of Roche, it is shown that Roche's payments under this Agreement were less than the royalty amount that should have been paid, then Roche will make all payments required to be made by paying Isis the difference between such amounts to eliminate any discrepancy revealed by said inspection with the next royalty payment due, with interest calculated in accordance with Section 6.15. If, as a result of any inspection of the books and records of Roche, it is shown that Roche's payments under this Agreement were greater than the royalty amount that should have been paid, then [***]. Isis will pay all fees charged by such accountant pursuant to the audit, *except that*, if the audit determines that any additional amounts payable by Roche for an audited period exceed [***] of the amount actually paid for such audited period, then, in addition to paying Isis any unpaid amounts discovered in such audit, Roche will pay the fees and expenses charged by such accountant.

**6.14.** **Taxes**.

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

**6.14.2.** **Withholding Tax**. To the extent the paying Party is required to deduct and withhold taxes on any payment, the paying Party will pay the amounts of such taxes to the proper governmental authority for the account of the receiving Party and remit the net amount to the receiving Party in a timely manner. The paying Party will promptly furnish the receiving Party with proof of payment of such taxes. If documentation is necessary in order to secure an exemption from, or a reduction in, any withholding taxes, the Parties will provide such documentation to the extent they are able to do so. In accordance with the procedures set forth in Section 9.3, the receiving Party will also indemnify the paying Party for any tax, interest or penalties imposed on the paying Party if the paying Party improperly reduces or eliminates withholding tax based upon representations made by the receiving Party.

**6.14.3.** **Tax Cooperation**. At least fifteen (15) days prior to the date a given payment is due under this Agreement, the non-paying Party will provide the paying Party with any and all tax forms that may be reasonably necessary in order for the paying Party to lawfully not withhold tax or to withhold tax at a reduced rate with



respect to such payment under an applicable bilateral income tax treaty. Following the paying Party's timely receipt of such tax forms from the non-paying Party, the paying Party will not withhold tax or will withhold tax at a reduced rate under an applicable bilateral income tax treaty, if appropriate under the Applicable Laws. The non-paying Party will provide any such tax forms to the paying Party upon request and in advance of the due date. Each Party will provide the other with reasonable assistance to enable the recovery, as permitted by Applicable Law, of withholding taxes resulting from payments made under this Agreement, such recovery to be for the benefit of the Party who would have been entitled to receive the money but for the application of withholding tax under this Section 6.14.

The provisions of this Section 6.14 are to be read in conjunction with the provisions of Section 12.4 below.

**6.15.** **Interest**. Any undisputed payments to be made hereunder that are not paid on or before the date such payments are due under this Agreement will bear interest at a rate per annum equal to the lesser of (i) one month LIBOR rate in effect on the date that such payment would have been first due plus two percentage points (2%) or (ii) the maximum rate permissible under applicable law.

## ARTICLE 7.
## INTELLECTUAL PROPERTY

**7.1.** **Ownership**.

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

**7.1.2.** **Agreement Technology**. Each Party will promptly disclose to the other Party in writing, and will cause its Affiliates to so disclose, the discovery, development, or creation of any invention made solely or jointly by the Parties in connection with the performance of obligations under this Agreement. Except as expressly provided in this Agreement, neither Party will have any obligation to account to the other for profits with respect to, or to obtain any consent of the other Party to license or exploit, Jointly-Owned Collaboration Technology by reason of joint ownership thereof, and each Party hereby waives any right it may have under the laws of any jurisdiction to require any such consent or accounting.



**7.1.3.** **Joint Patent Committee**.

**(a)** The Parties will establish a "***Joint Patent Committee***" or "***JPC***." The JPC will serve as the primary contact and forum for discussion between the Parties with respect to intellectual property matters arising under this Agreement, and will cooperate with respect to the activities set forth in this ARTICLE 7. Isis' obligation to participate in the JPC will terminate upon the date Isis is no longer obligated to participate in the JSC. Thereafter, Isis will have the right, but not the obligation, to participate in JPC meetings. The JPC determines the invention classification for each invention arising under this Agreement. The classifications are (i) Brain Shuttle Collaboration Patents, (ii) Isis Product-Specific Patents, (iii) Jointly-Owned Collaboration Patents, (iv) Isis Core Technology Patents, and (v) Isis Manufacturing and Analytical Patents. In addition, with respect to the Brain Shuttle Collaboration Patents classification, the JPC will determine the following sub-categories of Brain Shuttle Collaboration Patents: (w) Patent Rights claiming inventions solely related to the Brain Shuttle Technology ("***Brain Shuttle-Specific Collaboration Patents***"); (x) Patent Rights claiming inventions solely related to ASOs that do not utilize the Brain Shuttle Technology ("***ASO-Specific Collaboration Patents***"); (y) Patent Rights claiming inventions solely related to the linking or conjugation of molecules ("***Linker-Specific Collaboration Patents***"); and (z) Patent Rights claiming more than one of the technologies described in items (w) through (y) above ("***Omnibus Collaboration Patents***"). The JPC will endeavor to separate the claims within such Patent Rights into separate and distinct patent applications corresponding with the categories and sub-categories described in this Section 7.1.3(a) to the extent possible without diminishing the patentability of the inventions.

**(b)** A strategy will be discussed with regard to (x) prosecution and maintenance, defense and enforcement of (A) Brain Shuttle Collaboration Patents, (B) Isis Product-Specific Patents, and (C) Jointly-Owned Collaboration Patents licensed to Roche under Section 4.1.1 in connection with a Product, (y) defense against allegations of infringement of Third Party Patent Rights, and (z) licenses to Third Party Patent Rights or Know-How (including whether to obtain any licenses under any such Third-Party Patent Rights or Know-How, and whether there are any known Third Party Obligations applicable to a particular Product), in each case to the extent such matter would be reasonably likely to have a material impact on the Agreement or the licenses granted hereunder, which strategy will be considered in good faith by the Party entitled to prosecute, enforce and defend such Patent Rights hereunder, but will not be binding on such Party. Notwithstanding the above, subject to the provisions of Section 6.11, Roche shall have final say as to whether to obtain any licenses under Third-Party Patent Rights or Know-How.



**(c)** In addition, the Joint Patent Committee will be responsible for the determination of inventorship. The determination of inventorship will be in accordance with United States patent laws and therefore will determine if the invention is solely or jointly

owned by the relevant Party or Parties. In case of a dispute in the Joint Patent Committee (or otherwise between Isis and Roche) over inventorship or classification, if the Joint Patent Committee cannot resolve such dispute, even after seeking the JSC's input, such dispute will be resolved by independent patent counsel not engaged or regularly employed in the past two years by either Party and reasonably acceptable to both Parties. The decision of such independent patent counsel will be binding on the Parties. Expenses of such patent counsel will be shared equally by the Parties.

**(d)** The JPC will comprise an equal number of members from each Party. The Joint Patent Committee will meet as often as agreed by them (and at least semi-Annually), to discuss matters arising out of the activities set forth in this ARTICLE 7. The JPC will determine by unanimous consent the JPC operating procedures at its first meeting. To the extent reasonably requested by either Party, the Joint Patent Committee will solicit the involvement of more senior members of their respective legal departments with respect to critical issues. Each Party's representatives on the Joint Patent Committee will consider comments and suggestions made by the other in good faith. If either Party deems it reasonably advisable, the Parties will enter into a mutually agreeable common interest agreement covering the matters contemplated by this Agreement.

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

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

**7.2.2. Licensed Patents and Roche Patents**.

**(a) Licensed Patents**.

**(i) Isis Core and Manufacturing Patents**. Isis will at all times control and be responsible for all aspects of (i) any Brain Shuttle Collaboration Patents solely-owned by Isis that (A) include claims that are directed to subject matter applicable to ASOs in general, or (B) include an ASO, the sequence of which targets the RNA that encodes HTT and ASOs that do not target the RNA encoding HTT (each, an "***Isis Core Brain Shuttle Collaboration Patent***"), (ii) the Isis Core Technology Patents, and (iii) the Isis Manufacturing and Analytical Patents.



**(ii) Isis Product-Specific Patents**.

**(1)** ***Before Option Exercise***. Before Option exercise, subject to Section 7.2.3 and Section 7.2.4, at Isis' expense, Isis will control and be responsible for all aspects of the Prosecution and Maintenance of all (x) Brain Shuttle Collaboration Patents solely-owned by Isis that are necessary or useful to Develop or Commercialize a Product eligible to be licensed to Roche under Section 4.1.1 and *are not* necessary or useful to develop or commercialize products that are not Products (each, an "***Isis Product-Specific Brain Shuttle Collaboration Patent***"), and (y) Isis Product-Specific Patents, and will use commercially reasonably efforts to Prosecute and Maintain such Patent Rights.

**(2)** ***After Option Exercise***. After Option exercise, subject to Section 7.2.3 and Section 7.2.4, at Roche's expense, Roche will control and be responsible for all aspects of the Prosecution and Maintenance of all Isis Product-Specific Brain Shuttle Collaboration Patents and Isis Product-Specific Patents Covering Products licensed to Roche under Section 4.1.1 and will either (i) use commercially reasonably efforts to Prosecute and Maintain such Patent Rights or (ii) offer to assign Roche's entire right, title and interest in such Patent Rights to Isis, in which case following any such assignment all licenses granted in this Agreement by Isis to Roche under such Patent Rights shall become non-exclusive and the exclusivity covenants under Section 2.1.1 will no longer apply to such Patent Rights.

**(b) Roche Patents and Roche Brain Shuttle Collaboration Patents**. Roche will control and be responsible for all aspects of the Prosecution and Maintenance of all (i) Brain Shuttle Collaboration Patents solely-owned by Roche, and (ii) Roche Patents, subject to Section 7.2.3 and Section 7.2.4.

**7.2.3. Jointly-Owned Collaboration Patents**.

**(a)** ***Before Option Exercise***. Before Option exercise, (i) Isis will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Collaboration Patents Covering Isis Development Candidates, and (ii) Roche will control and be responsible for all aspects of the Prosecution and Maintenance of any Jointly-Owned Collaboration Patents Covering Brain Shuttle Development Candidates.



**(b)** ***After Option Exercise***. After Option exercise, Roche will control and be responsible for all aspects of the Prosecution and Maintenance of (i) Jointly-Owned Collaboration Patents Covering Products, and (ii) jointly-owned Brain Shuttle Collaboration Patents, and will either (y) use commercially reasonably efforts to Prosecute and Maintain such Patent Rights or (z) offer to assign Roche's entire right, title and interest in such Patent Rights to Isis, in which case following any such assignment all licenses granted in this Agreement by Isis to Roche under such Patent Rights shall become non-exclusive and the exclusivity covenants under Section 2.1.1 will no longer apply to such Patent Rights.

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

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

**(b)** If Roche elects (a) not to file and prosecute patent applications for the Jointly-Owned Collaboration Patent or Isis Product-Specific Patents that have been licensed to Roche under this Agreement or the Brain Shuttle Collaboration Patents for which Roche has responsibility for Prosecution and Maintenance pursuant to Section 7.2.2 or Section 7.2.3 ("***Roche-Prosecuted Patents***") in a particular country, (b) not to continue the prosecution (including any interferences, oppositions, reissue proceedings, re-examinations, and patent term extensions, adjustments, and restorations) or maintenance of any Roche-Prosecuted Patent in a particular country, or (c) not to file and prosecute patent applications for the Roche-Prosecuted Patent in a particular country following a written request from Isis to file and prosecute in such country, then Roche will so notify Isis promptly in writing of its intention in good time to enable Isis to meet any deadlines by which an action must be taken to establish or preserve any such Patent Right in such country; and Isis will have the right, but not the obligation, to file, prosecute, maintain, enforce, or otherwise pursue such Roche-Prosecuted Patent in the applicable country at its own expense with counsel of its own choice. In such case, Roche will cooperate with Isis to file for, or continue to Prosecute and



Maintain or enforce, or otherwise pursue such Roche-Prosecuted Patent in such country in Isis' own name. Notwithstanding anything to the contrary in this Agreement, if Isis assumes responsibility for the Prosecution and Maintenance of any such Roche-Prosecuted Patent under this Section 7.2.4(b), Isis will have no obligation to notify Roche if Isis intends to abandon such Roche-Prosecuted Patent. The analogous situation shall apply *mutatis mutandis* with regard to Patent Rights (excluding Isis Core Technology Patents and Isis Manufacturing and Analytical Patents) for which Isis has responsibility for Prosecution and Maintenance pursuant to Section 7.2.2 or Section 7.2.3.

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

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

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



**7.3. Patent Costs**.

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

**7.3.2. Licensed Patents and Roche Patents**. Except as set forth in Section 7.2.4 and Section 7.3.1, each Party will be responsible for all Patent Costs incurred by such Party prior to and after the Effective Date in all countries in the Prosecution and Maintenance of Patent Rights for which such Party is responsible under Section 7.2; *provided, however*, that after Option exercise, Roche will be solely responsible for Patent Costs arising from the Prosecution and Maintenance of the Isis Product-Specific Patents; *provided that*, Roche may decline to pay for filing, prosecuting and maintaining any Isis Product-Specific Patents in a particular country or particular countries, in which case all licenses granted in this Agreement by Isis to Roche under such Patent Rights shall become non-exclusive and the exclusivity covenants under Section 2.1.1 will no longer apply to such Patent Rights.

**7.4. Defense of Claims Brought by Third Parties**.

**7.4.1.** If a Third Party initiates a Proceeding claiming a Patent Right owned by or licensed to such Third Party is infringed by the Development, Manufacture or Commercialization of a Product, (a) Isis will have the first right, but not the obligation, to defend against any such Proceeding initiated prior to Option exercise at its sole cost and expense and (b) Roche will have the first right, but not the obligation, to

defend against any such Proceeding initiated after Option exercise at its sole cost and expense. If the Party having the first right to defend against such Proceeding (the "***Lead Party***") elects to defend against such Proceeding, then the Lead Party will have the sole right to direct the defense and to elect whether to settle such claim (but only with the prior written consent of the other Party, not to be unreasonably withheld, conditioned or delayed). The other Party will reasonably assist the Lead Party in defending such Proceeding and cooperate in any such litigation at the request and expense of the Lead Party. The Lead Party will provide the other Party with prompt written notice of the commencement of any such Proceeding that is of the type described in this Section 7.4, and the Lead Party will keep the other Party apprised of the progress of such Proceeding. If the Lead Party elects not to defend against a Proceeding, then the Lead Party will so notify the other Party in writing within sixty (60) days after the Lead Party first receives written notice of the initiation of such Proceeding, and the other Party (the "***Step-In Party***") will have the right, but not the obligation, to defend against such Proceeding at its sole cost and expense and thereafter the Step-In Party will have the sole right to direct the defense thereof, including the right to settle such claim. In any event, the Party not defending such



Proceeding will reasonably assist the other Party and cooperate in any such litigation at the request and expense of the Party defending such Proceeding. Each Party may at its own expense and with its own counsel join any defense initiated or directed by the other Party under this Section 7.4. Each Party will provide the other Party with prompt written notice of the commencement of any such Proceeding under this Section 7.4, and such Party will promptly furnish the other Party with a copy of each communication relating to the alleged infringement that is received by such Party.

**7.4.2.** **Discontinued Product**. If a Third Party initiates a Proceeding claiming that any Patent Right or Know-How owned by or licensed to such Third Party is infringed by the Development, Manufacture or Commercialization of a Discontinued Product, Isis will have the first right, but not the obligation, to defend against and settle such Proceeding at its sole cost and expense. Roche will reasonably assist Isis in defending such Proceeding and cooperate in any such litigation at the request and expense of Isis. Each Party may at its own expense and with its own counsel join any defense directed by the other Party. Isis will provide Roche with prompt written notice of the commencement of any such Proceeding, or of any allegation of infringement of which Isis becomes aware and that is of the type described in this Section 7.4.2, and Isis will promptly furnish Roche with a copy of each communication relating to the alleged infringement received by Isis.

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

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

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



cases of Competitive Infringement under Section 7.5.7 below, such written notice will be given within ten (10) Business Days.

**7.5.2.** **Prior to Option Exercise**. For any Competitive Infringement occurring after the Effective Date but before Option exercise, Isis will have the first right, but not the obligation, to institute, prosecute, and control a Proceeding with respect thereto, by counsel of its own choice, and Roche will have the right to be represented in that action by counsel of its own choice at its own expense, *however*, Isis will have the sole right to control such litigation. Isis will provide Roche with prompt written notice of the commencement of any such Proceeding, and Isis will keep Roche apprised of the progress of such Proceeding. If Isis fails to initiate a Proceeding within a period of ninety (90) days after receipt of written notice of such Competitive Infringement (subject to a ninety (90) day extension to conclude negotiations, which extension will apply only in the event that Isis has commenced good faith negotiations with an alleged infringer for elimination of such Competitive Infringement within such ninety (90) day period), Roche will have the right to initiate and control a Proceeding with respect to such Competitive Infringement by counsel of its own choice; *provided that* Isis will have the right to be represented in any such action by counsel of its own choice at its own expense. Notwithstanding the foregoing, Isis will at all times have the sole right to institute, prosecute, and control any Proceeding under this Section 7.5.2 to the extent involving any Isis Core Technology Patents or Isis Manufacturing and Analytical Patents.

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

any Proceeding under this Section 7.5.3 to the extent involving any Isis Core Technology Patents or Isis Manufacturing and Analytical Patents.



**7.5.4. Joinder**.

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

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

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

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

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

**(c)** any remaining proceeds constituting direct or actual damages for acts of infringement occurring after Roche's exercise of the Option will be treated [***], and [***]; then

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

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

**7.5.7. 35 USC 271(e)(2) Infringement**. Notwithstanding anything to the contrary in this Section 7.5, solely with respect to Licensed Patents, for a Competitive Infringement under 35 USC 271(e)(2), the time period set forth in Section 7.5.2 during which a Party will have the initial right to bring a Proceeding will be shortened to a total of twenty-five (25) days, so that, to the extent the other Party



has the right, pursuant to such Section to initiate a Proceeding if the first Party does not initiate a Proceeding, such other Party will have such right if the first Party does not initiate a Proceeding within twenty-five (25) days after such first Party's receipt of written notice of such Competitive Infringement.

**7.6. Other Infringement**.

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

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

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

**7.7. Patent Listing**.

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

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

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

**7.9.** **Obligations to Third Parties**. Notwithstanding any of the foregoing, each Party's rights and obligations with respect to Licensed Technology under this ARTICLE 7 will be subject to the Third Party rights and obligations under any (i) Third Party agreements the restrictions and obligations of which Roche has agreed to under Section 6.11.2(b), (ii) Prior Agreements, and (iii) Isis In-License Agreements; *provided, however*, that, to the extent that Isis has a non-transferable right to prosecute, maintain or enforce any Patent Rights licensed to Roche hereunder and, this Agreement purports to grant any such rights to Roche, Isis will act in such regard with respect to such Patent Rights at Roche's direction.

**7.10.** **Additional Right and Exceptions**. Notwithstanding any provision of this ARTICLE 7, but subject to Section 7.4.3, Isis retains the sole right to Prosecute and Maintain Isis Core Technology Patents and Isis Manufacturing and Analytical Patents during the Agreement Term and to control any enforcement of Isis Core Technology Patents and Isis Manufacturing and Analytical Patents, and will take the lead on such enforcement solely to the extent that the scope or validity of any Patent Rights Controlled by Isis and Covering the Isis Core Technology Patents or Isis Manufacturing and Analytical Patents is at risk. If Isis determines, in Isis' sole discretion, to not enforce any Isis Core Technology Patents or Isis Manufacturing and Analytical Patents and does not permit Roche to so enforce such Patent Rights, then the Parties will mutually agree on an appropriate adjustment (if any) of the future consideration payable by Roche under this Agreement to reflect any adverse impact Isis' failure to enforce such Patent Rights has on Products.

**7.11.** **Patent Term Extension**. The Parties will cooperate with each other in gaining patent term extension wherever applicable to a Product, including European supplementary protection certificates and pediatric exclusivity. After exercising the Option, Roche will determine which patents will be extended and what extensions will be sought.



**7.12.** **No Challenge**. If, during the Agreement Term, solely with respect to rights to the Licensed Patents that are included (or, prior to Option exercise, are eligible to be included) in a license granted to Roche under Section 4.1.1, Roche, its Affiliates or Sublicensees, in the United States or any other country, (a) commence or otherwise voluntarily determine to participate in (other than as may be necessary or reasonably required to assert a cross-claim or a counter-claim or to respond to a court request or order or administrative law request or order) any action or proceeding, challenging or denying the enforceability or validity of any claim within an issued patent or patent application within such Licensed Patents, or (b) direct, support or actively assist any other Person (other than as may be necessary or reasonably required to assert a cross-claim or a counter-claim or to respond to a court request or order or administrative law request or order) in bringing or prosecuting any action or proceeding challenging or denying the validity of any claim within an issued patent or patent application within such Licensed Patents, then unless, within thirty (30) days after written notice from Isis, Roche rescinds any actions brought by Roche, its Affiliates, or Sublicensees, Isis may terminate this Agreement and the provisions of Section 10.4.1 and Section 10.4.2 will apply; [***].

## ARTICLE 8.
## REPRESENTATIONS AND WARRANTIES

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

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

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

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

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

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

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

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

**8.2.1.** To the best of its knowledge and belief, there are no additional licenses (beyond those that would be granted to Roche under Section 4.1.1 upon the exercise of the Option for a Product arising under the Isis Development Candidate-R&D Plan) under any intellectual property owned or Controlled by Isis or its Affiliates as of the Effective Date that would be required in order for Roche to further Develop and Commercialize a Product arising under the Isis Development Candidate-R&D Plan existing on the Effective Date.

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

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



**8.2.4.** SCHEDULE 8.2.4(a), SCHEDULE 8.2.4(b) and SCHEDULE 8.2.4(c) set forth true, correct and complete lists of all Isis Core Technology Patents, Isis Manufacturing and Analytical Patents, and Isis Product-Specific Patents that apply to the Compounds contemplated under the Isis Development Candidate-R&D Plan as of the Effective Date, respectively, and indicates whether each such Patent Right is owned by Isis or licensed by Isis from a Third Party and if so, identifies the licensor or sublicensor from which the Patent Right is licensed. Isis Controls such Patent Rights existing as of the Effective Date and is entitled to grant all rights and licenses (or sublicenses, as the case may be) under such Patent Rights it purports to grant to Roche under this Agreement.

**8.2.5.** (a) There is no fact or circumstance known by Isis that would cause Isis to reasonably conclude that any Licensed Patent is invalid or un-enforceable, (b) there is no fact or circumstance known by Isis that would cause Isis to reasonably conclude the inventorship of each Licensed Patent is not properly identified on each patent, (c) all official fees, maintenance fees and annuities for the Licensed Patents have been paid and all administrative procedures with governmental agencies have been completed, (d) none of the Isis Product-Specific Patents that would be licensed by Isis to Roche upon Option exercise under this Agreement are currently involved in any interference, reissue, re-examination, cancellation or opposition proceeding and neither Isis, nor any of its Affiliates, has received any written notice from any person, or has knowledge, of such actual or threatened proceeding, and (e) to the best of Isis' knowledge and belief, Roche's practice of the inventions claimed in the Isis Product-Specific Patents in the performance of the Roche R&D Activities contemplated as of the Effective Date will not [***].

**8.2.6.** SCHEDULE 6.11.1 sets forth true, correct and complete lists of all Isis In-License Agreements relating to Licensed Technology necessary or useful to conduct the research, Development, Manufacture or Commercialization of Compounds as contemplated under the Isis Development Candidate-R&D Plan existing on the Effective Date. All Isis In-License Agreements are in full force and effect and have not been modified or amended. Neither Isis nor, to the best knowledge of Isis, the Third Party licensor in an Isis In-License Agreement is in default with respect to a material obligation under such Isis In-License Agreement, and neither such party has claimed or has grounds upon which to claim that the other party is in default with respect to a material obligation under, any Isis In-License Agreement.

**8.2.7.** SCHEDULE 8.2.7 is a complete and accurate list of all agreements that create Third Party Obligations that affect the rights granted by Isis to Roche under this Agreement with respect to Isis Development Candidates contemplated by the R&D Plans on the Effective Date.

**8.2.8.** Isis has all rights necessary to grant the option and licenses contained in this Agreement, and has the ability to work exclusively with Roche as set forth in this Agreement, including the covenants granted in Section 2.1.



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

**8.3.1.** Isis will promptly amend SCHEDULE 8.2.4(a), SCHEDULE 8.2.4(b) and SCHEDULE 8.2.4(c) and submit such amended Schedules to Roche if Isis becomes aware that any Isis Core Technology Patents, Isis Manufacturing and Analytical Patents or Isis Product-Specific Patents are not properly identified on such Schedule.

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

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

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

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

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

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

**8.3.8.** If, after the Effective Date, Isis becomes the owner or otherwise acquires Control of any formulation or delivery technology that would be necessary or useful in order for Roche to further Develop, Manufacture or Commercialize a Product, and Roche has exercised its Option and the license granted to Roche under this Agreement is in effect, Isis will make such technology available to Roche on commercially reasonable terms.

**8.4.** **Representations and Warranties of Roche**. Roche hereby represents and warrants to Isis, as of the Effective Date, that:



**8.4.1.** SCHEDULE 8.4.1 sets forth a true and correct list of Patent Rights owned or Controlled as of the Effective Date by Roche or its Affiliates that (i) specifically claim Roche's Brain Shuttle technology, or (ii) are necessary or useful for the research, Development or Commercialization of a Brain Shuttle Development Candidate (such Patent Rights, "***Roche Existing Brain Shuttle Patents***"). Roche Controls such Roche Existing Brain Shuttle Patents existing as of the Effective Date and is entitled to grant all rights and licenses (or sublicenses, as the case may be) under such Roche Existing Brain Shuttle Patents it purports to grant to Isis under this Agreement; and

**8.4.2.** (a) There is no fact or circumstance known by Roche that would cause Roche to reasonably conclude that any Roche Existing Brain Shuttle Patent is invalid or un-enforceable, (b) there is no fact or circumstance known by Roche that would cause Roche to reasonably conclude the inventorship of each Roche Existing Brain Shuttle Patent is not properly identified on each patent, (c) all official fees, maintenance fees and annuities for the Roche Existing Brain Shuttle Patents have been paid and all administrative procedures with governmental agencies have been completed, (d) none of the Roche Existing Brain Shuttle Patent are currently involved in any interference, reissue, re-examination, cancellation or opposition proceeding and neither Isis, nor any of its Affiliates, has received any written notice from any person, or has knowledge, of such actual or threatened proceeding, and (e) to the best of Roche's knowledge and belief, Isis' practice of the inventions claimed in the Roche Existing Brain Shuttle Patents in the performance of the Isis R&D Activities contemplated as of the Effective Date will not infringe the Patent Rights of any Third Party.

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

## ARTICLE 9.
## INDEMNIFICATION; INSURANCE

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



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

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

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

**9.1.4.** the Commercialization of a Product by or on behalf of Roche or its Affiliates or Sublicensees;

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

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

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

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

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

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

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



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

**9.4.** **Insurance**.

**9.4.1.** **Isis' Insurance Obligations**. Isis will maintain, at its cost, reasonable insurance against liability and other risks associated with its activities contemplated by this Agreement, including but not limited to its indemnification obligations herein, in such amounts and on such terms as are customary for prudent practices for biotech companies of similar size and with similar resources in the pharmaceutical industry for the activities to be conducted by it under this Agreement taking into account the scope of development of products. Isis will furnish to Roche evidence of any insurance required under this Section 9.4.1, upon request.

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

**9.5.** **LIMITATION OF CONSEQUENTIAL DAMAGES**. **EXCEPT FOR (a) CLAIMS OF A THIRD PARTY THAT ARE SUBJECT TO INDEMNIFICATION UNDER THIS ARTICLE 9, (b) CLAIMS ARISING OUT OF A PARTY'S WILLFUL MISCONDUCT OF THIS AGREEMENT, (c) A PARTY'S BREACH OF ARTICLE 2, OR A BREACH OF SECTION 10.4.1(b) BY ROCHE OR ITS AFFILIATES OR (d) CLAIMS ARISING OUT OF A PARTY'S BREACH OF ITS CONFIDENTIALITY OBLIGATIONS UNDER THIS AGREEMENT, NEITHER PARTY NOR ANY OF ITS AFFILIATES WILL BE LIABLE TO THE OTHER PARTY TO THIS AGREEMENT OR ITS AFFILIATES FOR ANY INCIDENTAL, CONSEQUENTIAL, SPECIAL, PUNITIVE OR OTHER INDIRECT DAMAGES, WHETHER LIABILITY IS ASSERTED IN CONTRACT, TORT (INCLUDING NEGLIGENCE AND STRICT PRODUCT LIABILITY), INDEMNITY OR CONTRIBUTION, AND IRRESPECTIVE OF WHETHER THAT PARTY OR ANY REPRESENTATIVE OF THAT PARTY HAS BEEN ADVISED OF, OR OTHERWISE MIGHT HAVE ANTICIPATED THE POSSIBILITY OF, ANY SUCH LOSS OR DAMAGE.**



## ARTICLE 10.
## TERM; TERMINATION

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

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

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

**10.1.3.** where Roche has not provided Isis a written notice stating Roche is exercising its Option under Section 6.3 by the Option Deadline.

The period from the Effective Date until the date of expiration of this Agreement pursuant to this Section 10.1 is the "***Agreement Term***." On a Product-by-Product basis, if with respect to a particular Product this Agreement expires (i.e., is not terminated early) under Section 10.1.1 or Section 10.1.2 in a particular country, then, effective upon such expiration, Isis will and hereby does grant to Roche a fully paid-up and irrevocable non-exclusive license under the Licensed Technology to Manufacture, Develop and Commercialize the Product that is the subject of such expiration in such country.

**10.2. Termination of the Agreement**.

**10.2.1. Roche's Termination for Convenience**. After payment by Roche of the upfront fee under Section 6.1, subject to Section 10.4.1 below, Roche may terminate this Agreement for convenience by providing ninety (90) days written notice to Isis of such termination. If Roche terminates this Agreement for convenience under this Section 10.2.1 prior to Roche paying Isis the milestone payment for achievement of the Initiation of a Phase 1 Trial Milestone Event, then if (i) Isis continues to develop the Product after such termination and achieves the Initiation of the Phase 1 Trial Milestone Event for such Product, and (ii) Isis has not granted a Third Party an exclusive license or an exclusive option to obtain an exclusive license to such Product by the [***], then [***], unless by that time Isis has undergone or has agreed to a Change of Control, in which case no such payment shall be due or payable.



**10.2.2. Termination for Material Breach**.

**(a) Roche's Right to Terminate**. If Roche believes that Isis is in material breach of this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under ARTICLE 1, which is governed by Section 10.2.3 below), then Roche may deliver notice of such material breach to Isis. If the breach is curable, Isis will have sixty (60) days to cure such breach. If Isis fails to cure such breach within the sixty (60) day period, or if the breach is not subject to cure, Roche may terminate this Agreement by providing written notice to Isis.

**(b) Isis' Right to Terminate**. If Isis believes that Roche is in material breach of this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under ARTICLE 1 or Section 5.1, which is governed by Section 10.2.3 below), then Isis may deliver notice of such material breach to Roche. If the breach is curable, Roche will have sixty (60) days to cure such breach (except to the extent such breach involves the failure to make a payment when due, which breach must be cured within thirty (30) days following such notice). If Roche fails to cure such breach within the sixty (60) day or thirty (30) day period, as applicable, or if the breach is not subject to cure, Isis may terminate this Agreement by providing written notice to Roche.

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

**(a)** If Isis, in Roche's reasonable determination, fails to use Commercially Reasonable Efforts in the activities contemplated in ARTICLE 1 prior to Option exercise, Roche will notify Isis and, within thirty (30) days thereafter, Isis and Roche will meet and confer to discuss and resolve the matter in good faith, and attempt to devise a mutually agreeable plan to address any outstanding issues related to Isis' use of Commercially Reasonable Efforts in ARTICLE 1. Following such a meeting, if Isis fails to use Commercially Reasonable Efforts as contemplated by ARTICLE 1, then subject to Section 10.2.4 below, Roche will have the right, at its sole discretion, to (i) terminate this Agreement, or (ii) prior to Option exercise, Roche may elect to trigger the alternative remedy provisions of Section 10.3 below in lieu of terminating this Agreement by providing written notice to Isis. If Roche elects to trigger the alternative remedy provisions of Section 10.3 below, then such election is Roche's sole and exclusive remedy if Isis fails to use Commercially Reasonable Efforts in the activities contemplated in ARTICLE 1 prior to Option exercise.

**(b)** If Roche, in Isis' reasonable determination, fails to use Commercially Reasonable Efforts under ARTICLE 1 or Section 5.1 above, Isis will notify Roche and, within thirty (30) days thereafter, Isis and Roche will meet and confer to discuss and resolve the matter in good faith, and attempt to devise a mutually agreeable plan to address any outstanding



issues related to Roche's use of Commercially Reasonable Efforts in ARTICLE 1 or Section 5.1. Following such a meeting, if Roche fails to use Commercially Reasonable Efforts as contemplated by ARTICLE 1 or Section 5.1, then subject to Section 10.2.4 below, Isis will have the right, at its sole discretion, to terminate this Agreement.

**10.2.4. Disputes Regarding Material Breach**. Notwithstanding the foregoing, if the Breaching Party in Section 10.2.2 or Section 10.2.3 disputes in good faith the existence, materiality, or failure to cure of any such breach which is not a payment breach, and provides notice to the Non-Breaching Party of such dispute within such sixty (60) day period, the Non-Breaching Party will not have the right to terminate this Agreement in accordance with Section 10.2.2 or Section 10.2.3, or trigger the alternative remedy provisions of Section 10.3, as applicable, unless and until it has been determined in accordance with Section 12.1 that this Agreement was materially breached by the Breaching Party and the Breaching Party fails to cure such breach within thirty (30) days following such determination. It is understood and acknowledged that during the pendency of such dispute, all the terms of this Agreement will remain in effect and the Parties will continue to perform all of their respective obligations hereunder, including satisfying any payment obligations.

**10.2.5. Termination for Insolvency**.

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

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



**10.2.6. Termination if Development Candidate Not Identified**.

**(a)** ***Failure to Identify a Brain Shuttle Development Candidate***. If, despite the Parties' Commercially Reasonable Efforts, Roche has not designated at least one Brain Shuttle Development Candidate by the [***] of the Effective Date, then either Party will have the right to terminate this Agreement solely with respect to the Brain Shuttle Development Candidate-R&D Plan by providing written notice to the other Party within [***] of the Effective Date. In the case of termination of this Agreement under this Section 10.2.6(a), Section 10.4.1 will apply solely with respect to the Brain Shuttle Development Candidate-R&D Plan. Nothing in this Section 10.2.6(a) will terminate or otherwise affect the provisions of this Agreement with respect to the Isis Development Candidate-R&D Plan, which shall remain in full force and effect.

**(b)** ***Failure to Identify an Isis Development Candidate***. If, despite Isis' Commercially Reasonable Efforts, Isis has not designated at least one Isis Development Candidate by the [***] of the Effective Date, then either Party will have the right to terminate this Agreement with respect to the Isis Development Candidate-R&D Plan by providing written notice to the other Party within [***] of the Effective Date. In the case of termination of this Agreement under this Section 10.2.6(b), Section 10.4.1 will apply solely with respect to the Isis Development Candidate-R&D Plan. Nothing in this Section 10.2.6(b) will terminate or otherwise affect the provisions of this Agreement with respect to the Brain Shuttle Development Candidate-R&D Plan, which shall remain in full force and effect.

**10.3. Alternative Remedies to Termination Available to Roche Prior to Option Exercise**. If, prior to Option exercise, Roche elects to exercise the alternative remedy provisions of this Section 10.3 in lieu of terminating this Agreement by providing written notice of such election to Isis in accordance with Section 10.2.3(a), then this Agreement will continue in full force and effect with the following modifications:

**(a)** Isis will have no further obligations under the R&D Plans, and Roche is responsible for the continued research, Development and Commercialization of Products (including meeting all remaining performance obligations under ARTICLE 1 and Section 5.1);

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



**(c)** Roche will have and Isis grants, the exclusive license under Section 4.1.1;

**(d)** Isis will perform its obligations under Section 4.2 within sixty (60) days of Roche electing to exercise its alternative remedies under this Section 10.3; and

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

**(i)** [***] *Payments*. Roche will [***]; and

**(ii)** *License Fee*. The license fee set forth in Section 6.3 will be [***]. Such [***] will be due within [***] after the [***] but in no event later than [***].

The milestone provisions of Section 6.4 and Section 6.5 and the royalty provisions of Section 6.7 will [***].

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

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

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

**(b)** **License Termination**. Except for the licenses granted under Section 4.1.2, any licenses granted by Isis to Roche under this Agreement will terminate and Roche, its Affiliates and Sublicensees will cease selling all Products.

**(c)** **Exclusivity Covenants**. Neither Party will have any further obligations under Section 2.1.1 of this Agreement.

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



**(e)** **Survival**. The following provisions of this Agreement will survive the expiration or termination of this Agreement: Section 1.12 (Failure to Designate an Isis Development Candidate) (but only if this Agreement is terminated under Section 10.2.6(b) with respect to the Isis Development Candidate-R&D Plan); Section 4.1.2 (Brain Shuttle IP Licenses); Section 4.1.4(d) (Effect of Termination on Sublicenses), Section 4.2 (Technology Transfer after Option Exercise) (but only to the extent necessary to satisfy the requirements of Section 10.4.2), Section 6.10 (Reverse Royalty Payments to Roche for a Discontinued Product), Section 6.12.5 (Records Retention), Section 6.13 (Audits), Section 7.1.1 (Isis Technology and Roche Technology), Section 7.1.2 (Agreement Technology), Section 8.5 (Disclaimer), ARTICLE 9 (Indemnification; Insurance), Section 10.1 (Agreement Term; Expiration), Section 10.2.1 (Roche's Termination for Convenience), Section 10.2.5 (Termination for Insolvency), Section 10.4 (Consequences of Expiration or Termination of the Agreement), ARTICLE 11 (Confidentiality), ARTICLE 12 (Miscellaneous) and APPENDIX 1 (Definitions) (to the extent definitions are embodied in the foregoing listed Articles and Sections).

**10.4.2.** **Special Consequences of Expiration or Termination of the Agreement**. If (A) this Agreement expires due to the expiration of Roche's Option under Section 3.2, (B) Roche terminates the Agreement under Section 10.2.1 (Roche's Termination for Convenience), or (C) Isis terminates this Agreement under Section 7.12 (No Challenge), Section 10.2.2(b) (Isis' Right to Terminate) or Section 10.2.3(b) (Remedies for Failure to Use Commercially Reasonable Efforts), then the following additional terms will also apply:

**(a)** ***License to Isis for Isis Development Candidates***. Roche will and hereby does grant to Isis a sublicensable, worldwide, exclusive license or sublicense, as the case may be, under all Roche Technology (excluding Companion Diagnostic IP) Controlled by Roche as of the date of such reversion that Covers Discontinued Products comprising an Isis Development Candidate solely as necessary to Develop, make, have made, use, sell, offer for sale, have sold, import and otherwise Commercialize such Discontinued Products in the Field;

**(b)** ***License to Isis for Brain Shuttle Development Candidates***. Roche will and hereby does grant to Isis a sublicensable, worldwide, non-exclusive license or sublicense, as the case may be, under all Roche Technology (excluding Companion Diagnostic IP) Controlled by Roche as of the date of such reversion that Covers Discontinued Products comprising a Brain Shuttle Development Candidate solely as necessary to Develop, make, have made, use, sell, offer for sale, have sold, import and otherwise Commercialize such Discontinued Products in the Field;



**(c)** ***License to Isis for Companion Diagnostic Products***. Roche will make available to Isis, on commercially reasonable terms, any diagnostic products and/or services to select patients who will use Products (each, a "***Companion Diagnostic Product***") and any Patent Rights and Know-How Covering such Companion Diagnostic Products (such intellectual property, "***Companion Diagnostic IP***") Controlled by Roche as of the date of such reversion that is necessary to Develop or Commercialize such Companion Diagnostic Products;

**(d)** ***Know-How Transfer***. Roche will transfer to Isis for use with respect to the Development and Commercialization of Discontinued Products, copies of any Know-How data, results, regulatory information, filings, and files in the possession of Roche as of the date of such reversion that relate to such Discontinued Products and are necessary for the Development of such Discontinued Products, and any other information or material specified in Section 4.2;

**(e)** ***Trademarks***. Roche will license to Isis any trademarks that are specific to Discontinued Products solely for use with such Discontinued Products; *provided, however*, that in no event will Roche have any obligation to license to Isis any trademarks used by Roche both in connection with a Product and in connection with the sale of any other product or service, including any Roche- or Roche-formative marks, company logos, or trademarks of its Affiliates or Sublicensees; and

**(f)** ***Prosecution and Maintenance***. Isis will control and be responsible at its sole cost for all aspects of the Prosecution and Maintenance of all Jointly-Owned Collaboration Patents, and Roche will provide Isis with (and will instruct its counsel to provide Isis with) all of the information and records in Roche's and its counsel's possession related to the Prosecution and Maintenance of such Jointly-Owned Collaboration Patents.

## ARTICLE 11.
## CONFIDENTIALITY

**11.1.** **Confidentiality; Exceptions**. Except to the extent expressly authorized by this Agreement or otherwise agreed in writing, the Parties agree that, during the Agreement Term and for five years thereafter, the receiving Party (the "***Receiving Party***") and its Affiliates will keep confidential and will not publish or otherwise disclose or use for any purpose other than as provided for in this Agreement any confidential or proprietary information or materials, patentable or otherwise, in any form (written, oral, photographic, electronic, magnetic, or otherwise) which is disclosed to it by the other

Party (the "***Disclosing Party***") or its Affiliates or otherwise received or accessed by a Receiving Party in the course of performing its obligations or exercising its rights under this Agreement, including trade secrets, Know-How, inventions or discoveries,



proprietary information, formulae, processes, techniques and information relating to the past, present and future marketing, financial, and research and development activities of any product or potential product or useful technology of the Disclosing Party or its Affiliates and the pricing thereof (collectively, "***Confidential Information***").

**11.2.** **Prior Confidentiality Agreement**. The Non-Disclosure Agreement executed by Isis and Roche on February 1, 2012 (including any and all amendments thereto) (the "***CDA***") will govern disclosures of Information (as defined in the CDA) between the Parties prior to the Effective Date. All Confidential Information exchanged between the Parties on or after the Effective Date under this Agreement will be subject to the terms of this ARTICLE 11.

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

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

**11.4.1.** **Public Announcements — Generally**. Upon execution of this Agreement, the Parties will issue a joint press release announcing the existence of this Agreement in a form and substance agreed to in writing by the Parties. Except to the extent required to comply with Applicable Law, regulation, rule or legal process or as otherwise permitted in accordance with this Section 11.4, each Party agrees not to issue any other press release or other public statement disclosing other information relating to this Agreement or the terms of this Agreement or the transactions contemplated hereby without the prior written consent of the other Party, which consent will not be unreasonably withheld or delayed.



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

**11.4.3.** **Notice of Significant Events**. Each Party will notify (no later than three Business Days after the information or results are obtained) the other Party of any significant event related to a Product (including any data, serious adverse event or regulatory advice or approval) so that the Parties may analyze the need to or desirability of publicly disclosing or reporting such event. Notwithstanding Section 11.4.1 above, any press release or other similar public communication by either Party related to a Product's efficacy or safety data and/or results, will be submitted to the other Party for review and approval at least three Business Days in advance of such proposed public disclosure, which approval will not be unreasonably withheld or delayed.

**11.4.4.** **Prior to Option Exercise**. Prior to Option exercise, Isis will have the sole right, consistent with its practice with its other compounds and products, to issue press releases, publish, present or otherwise disclose the progress and results regarding the Products to the public; *provided*, that with respect to any proposed press release or other similar public communication by Isis disclosing regulatory discussions, the efficacy or safety data or clinical results related to the Products, (i) Isis will submit such proposed communication to Roche for review at least ten (10) Business Days in advance of such proposed public disclosure, (ii) Roche will have the right to review and recommend changes to such communication, and (iii) Isis will in good faith consider any changes that are timely recommended by Roche.

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

**11.4.6.** **Scientific or Clinical Presentations**. Regarding any proposed scientific publications related to results from any Clinical Studies, the Parties agree to use Commercially Reasonable Efforts to control public scientific disclosures of such results to prevent any adverse effect of any premature public disclosure of such results. The Parties will establish a procedure for publication review and each

Party will first submit to the other Party through the Joint Patent Committee an early draft of all such publications or presentations, at least forty-five (45) days prior to submission for publication including to facilitate the publication of any summaries of Clinical Studies data and results as required on the clinical trial registry of each respective Party. Each Party will review such proposed publication to avoid the unauthorized disclosure of a Party's Confidential Information and to preserve the patentability of inventions arising from an R&D Plan. If, during such forty-five (45) day period, the other Party informs such Party that its proposed publication contains Confidential Information of the other Party, then such Party will delete such Confidential Information from its proposed publication. In addition, if during such forty-five (45) day period, the other Party informs such Party that its proposed publication discloses non-public inventions made by either Party in the course of the Development under this Agreement, or the public disclosure of such proposed publication may have a material adverse effect on any Patent Rights or Know-How solely owned or Controlled by such other Party, then such Party will either (i) delay such proposed publication for up to sixty (60) days from the date of such Party's objection, to permit the timely first filing of patent application(s), or (ii) remove the identified disclosures prior to publication.

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

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

**11.4.9** **Acknowledgment; Commercial Materials**. Each Party will acknowledge in any press release, public presentation, publication or commercial marketing materials regarding the collaboration or a Product, the other Party's role in discovering and developing a Product or Discontinued Product, as applicable, that the Product is under license from Isis and otherwise acknowledge the contributions from the other Party, and each Party's stock ticker symbol (e.g., Isis: Nasdaq: ISIS; Roche: SIX: RO, ROG; OTCQX: RHHBY). Isis may include the Products (and identify Roche as its partner for the Product) in Isis' drug pipeline.

## ARTICLE 12.
## MISCELLANEOUS

**12.1.** **Dispute Resolution**.

**12.1.1.** **Escalation**. If any dispute occurs under this Agreement (other than a dispute regarding the construction, validity or enforcement of either Party's Patents,



which disputes will be resolved pursuant to Section 12.2), either Party may request in writing that the dispute be referred for resolution to the Head of Roche Partnering of Roche and the COO of Isis (the "***Executives***"). Within thirty (30) days after such a request, the Executives will meet in person at a mutually acceptable time and location or by means of telephone or video conference to negotiate a settlement of the dispute. Each Party's JSC representatives may participate in such meeting if desired. If the Executives fail to resolve the dispute within such thirty (30) day period, then the dispute will be referred to binding arbitration under Section 12.1.2.

**12.1.2.** **Binding Arbitration**. If a dispute subject to Section 12.1.1 is not resolved pursuant to Section 12.1.1, such dispute will be resolved through binding arbitration in accordance with this Section 12.1.2 and under the Commercial Arbitration Rules of the American Arbitration Association ("***AAA***") then in effect, including application of the "*Expedited Procedures*" (sections E-1, et al) of the Commercial Arbitration Rules of the AAA. The proceedings and decisions of the arbitrator will be confidential, final and binding on the Parties, and judgment upon the award of such arbitrators may be entered in any court having jurisdiction thereof. The arbitration will take place in Boston, Massachusetts USA and will be conducted by three (3) arbitrators. Each of Roche and Isis shall appoint one (1) arbitrator within thirty (30) days after the notice that initiated the arbitration. These two (2) arbitrators shall in turn appoint a third arbitrator who will be reasonably acceptable to the Parties and who will be appointed in accordance with AAA rules. Each arbitrator chosen hereunder will have educational training and industry experience sufficient to demonstrate a reasonable level of scientific, financial, medical and industry knowledge relevant to the particular dispute.

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

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

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

**12.3.** **Remedies**. Notwithstanding anything to the contrary in this Agreement, each Party will be entitled to seek, in addition to any other right or remedy it may have, at law or in equity, a temporary restraining order or a preliminary injunction, without the posting of any bond or other security, enjoining or restraining the other Party from any violation or threatened violation of this Agreement, and the Parties agree that in the event of a threatened or actual material breach of this Agreement injunctive relief would be

appropriate. Neither Party may recover any Losses relating to any matter arising under one provision of this Agreement to the extent that such Party has already recovered Losses with respect to such matter pursuant to other provisions of this Agreement (including recoveries under Section 9.1 or Section 9.2). Except for the offsets and credits explicitly set forth in Section 6.11.3(b) and Section 6.13, neither Party will have the right to setoff any amount it is owed or believes it is owed against payments due or payable to the other Party under this Agreement.

**12.4.** **Assignment and Successors**. Neither this Agreement nor any obligation of a Party hereunder may be assigned by either Party without the consent of the other, except that each Party may assign this Agreement and the rights, obligations and interests of such Party, in whole or in part, without the other Party's consent, to any of its Affiliates, to any purchaser of all or substantially all of its assets or all or substantially all of its assets to which this Agreement relates or to any successor corporation resulting from any merger, consolidation, share exchange or other similar transaction; *provided*, if a Party transfers or assigns this Agreement to [***] described in this Agreement, then such transferring Party (or such Affiliate) ("***Transferring Party***"), will [***] that the Transferring Party is obligated to pay to the non-transferring Party ("***Non-Transferring Party***") under ARTICLE 6 for the taxes withheld such that the Non-Transferring Party receives [***] assignment. In addition, Isis may assign or transfer its rights to receive payments under this Agreement (but no liabilities), without Roche's consent, to an Affiliate or to a Third Party in connection with a payment factoring transaction. Any purported assignment or transfer made in contravention of this Section 12.4 will be null and void.

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

**12.5.** **Change of Control**. If Isis undergoes a Change of Control, then Roche shall have the right at any time after it exercises the Option to disband the JSC and make unilateral decisions with respect to the R&D Plan, Development and Commercialization with no obligation to seek input from Isis or its successor, if applicable.

**12.6.** **Force Majeure**. No Party will be held responsible to the other Party nor be deemed to be in default under, or in breach of any provision of, this Agreement for failure or delay in performing any obligation of this Agreement when such failure or delay is due to force majeure, and without the fault or negligence of the Party so failing or delaying. For purposes of this Agreement, force majeure means a cause beyond the reasonable control of a Party, which may include acts of God; acts, regulations, or laws of any government; war; terrorism; civil commotion; fire, flood, earthquake, tornado, tsunami, explosion or storm; pandemic; epidemic and failure of public utilities or common carriers. In such



event the Party so failing or delaying will immediately notify the other Party of such inability and of the period for which such inability is expected to continue. The Party giving such notice will be excused from such of its obligations under this Agreement as it is thereby disabled from performing for so long as it is so disabled for up to a maximum of ninety (90) days, after which time the Parties will negotiate in good faith any modifications of the terms of this Agreement that may be necessary to arrive at an equitable solution, unless the Party giving such notice has set out a reasonable timeframe and plan to resolve the effects of such force majeure and executes such plan within such timeframe. To the extent possible, each Party will use reasonable efforts to minimize the duration of any force majeure.

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

If to Isis, addressed to:
Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: Chief Operating Officer
Fax: 760-918-3592

with a copy to:
Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: General Counsel
Fax: 760-268-4922

If to Roche, addressed to:
F. Hoffmann-La Roche Ltd
Grenzacherstrasse 124
4070 Basel, Switzerland
Attention: Corporate Legal Department
Fax: +41 61 688 13 96

If to Roche, addressed to:
Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110
Attention: Corporate Secretary
Fax: 973-235-3500

with a copy to:
F. Hoffmann-La Roche Ltd
Grenzacherstrasse 124
4070 Basel, Switzerland
Attention: Alliance Manager
Fax: +41 61 688 30 50

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

**12.8.** **Invoices**. All invoices that are required or permitted hereunder shall be in writing and sent by Isis to Roche at the following address or any other address that Roche may later provide:

F. Hoffmann-La Roche AG
Kreditorenbuchhaltung
4070 Basel
Switzerland

with an electronic copy to Roche's Alliance Manager.

Upon Isis' request, Roche's Alliance Manager will provide Isis' Alliance Manager with any additional information reasonably requested by Isis to facilitate the prompt delivery of invoices to Roche, including a facsimile number for sending invoices.

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

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

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



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

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

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

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

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

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

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

*[SIGNATURE PAGES FOLLOW]*

* - * - * - *



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

**F. HOFFMANN-LA ROCHE LTD**

By: /s/ *Sophie Kornowski-Bonnet*
Name: Sophie Kornowski-Bonnet
Title: Global Head of Roche Partnering

By: /s/ *Stefan Arnold*
Name: Stefan Arnold
Title: Head Legal Pharma

**SIGNATURE PAGE TO HTT RESEARCH, DEVELOPMENT, OPTION AND LICENSE AGREEMENT**

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

**HOFFMANN-LA ROCHE INC.**

By: /s/ *John P. Parise*
Name: John P. Parise
Title: Authorized Signatory

**SIGNATURE PAGE TO HTT RESEARCH, DEVELOPMENT, OPTION AND LICENSE AGREEMENT**

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

**ISIS PHARMACEUTICALS, INC.**

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

**SIGNATURE PAGE TO HTT RESEARCH, DEVELOPMENT, OPTION AND LICENSE AGREEMENT**

## LIST OF APPENDICES AND SCHEDULES

## APPENDIX 1

## DEFINITIONS

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

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

"***Additional Core IP***" has the meaning set forth in Section 6.11.3(a).

"***Additional Costs***" means [***].

"***Additional Isis Development Candidate-Cost Estimate***" has the meaning set forth in Section 1.8.3.

"***Additional Isis In-License Agreements***" has the meaning set forth in Section 6.11.1(b).

"***Additional Product-Specific Patents***" has the meaning set forth in Section 6.11.2(a).

"***Affiliate***" of an entity means any corporation, firm, partnership or other entity which directly or indirectly through one or more intermediaries controls, is controlled by or is under common control with a Party to this Agreement. An entity will be deemed to control another entity if it (i) owns, directly or indirectly, more than fifty percent (50%) of the outstanding voting securities or capital stock (or such lesser percentage which is the maximum allowed to be owned by a foreign corporation in a particular jurisdiction) of such other entity, or has other comparable ownership interest with respect to any entity other than a corporation; or (ii) has the power, whether pursuant to contract, ownership of securities or otherwise, to direct the management and policies of the entity. Anything to the contrary in this paragraph notwithstanding, Chugai Pharmaceutical Co., Ltd, a Japanese corporation ("Chugai"), shall not be deemed an Affiliate of Roche unless Roche provides written notice to Isis of its desire to include Chugai as an Affiliate of Roche.

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

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

"***Alliance Manager***" has the meaning set forth in Section 1.5.3.

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

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



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

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

"***Approval***" means (i) with respect to a Product in the EU, the earlier to occur of (A) approval from the applicable Regulatory Authority in at least one member state in the EU sufficient for the manufacture, distribution, use, marketing and sale of such Product, including pricing and reimbursement approval, in such jurisdiction in accordance with Applicable Laws, or (B) the First Commercial Sale of a Product in the EU; and (ii) with respect to a Product in any regulatory jurisdiction other than the EU, approval sufficient for the manufacture, distribution, use, marketing and sale of such Product in such jurisdiction in accordance with Applicable Laws.

"***Approved Changes***" means any changes (including number of subjects, duration of dosing, additional studies, additional endpoints, additional analysis, etc.) to the Isis Development Candidate-R&D Plan that are agreed to by Roche (including any changes required by a Regulatory Authority).

"***AS ASO***" has the meaning set forth in Section 2.1.1(b)(ii).

"***AS Development Candidate***" has the meaning set forth in Section 2.1.1(b)(ii).

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

"***ASO-Specific Collaboration Patents***" has the meaning set forth in Section 7.1.3(a).

"***Audit Report***" has the meaning set forth in Section 6.13.

"***Back-Up Compound***" means a Compound (other than the first Development Candidate) that was used in any monkey tolerability screen performed to identify the first Development Candidate.

"***Bankruptcy Code***" has the meaning set forth in Section 10.2.5(b).

"***Brain Shuttle***" has the meaning set forth in Section 1.1.

"***Brain Shuttle Collaboration Patents***" means Patent Rights arising under the Brain Shuttle Development Candidate-R&D Plan after the Effective Date that are Controlled by a Party or any of its Affiliates. The Parties will list on APPENDIX 6 the Brain Shuttle Collaboration Patents, and will update APPENDIX 6 when additional Brain Shuttle Collaboration Patents arise under the Brain Shuttle Development Candidate-R&D Plan.

"***Brain Shuttle Development Candidate***" has the meaning set forth in Section 1.3.1.

"***Brain Shuttle Development Candidate-R&D Plan***" means the research and development plan attached hereto as APPENDIX 3 (as may be amended in accordance with this Agreement) to conduct the Isis R&D Activities and Roche R&D Activities designated under such plan focused on the research and development of a Brain Shuttle Development Candidate.



"***Brain Shuttle Development Candidate Reverse Royalties***" has the meaning set forth in Section 6.10.2.

"***Brain Shuttle Program Cost Estimate***" has the meaning set forth in Section 1.6.2(b)(i).

"***Brain Shuttle-Specific Collaboration Patents***" has the meaning set forth in Section 7.1.3(a).

"***Brain Shuttle Technology***" means the Brain Shuttle technology disclosed in the Roche Existing Brain Shuttle Patents listed on Schedule 8.4.1 or otherwise existing as of the Effective Date as evidenced by Roche's written records.

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

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

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

"***Calendar Year***" means a year beginning on January 1 (or, with respect to 2013, the Effective Date) and ending on December 31.

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

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

"***Change of Control***" means, with respect to a Party: (a) the acquisition by any Third Party of beneficial ownership of more than fifty percent (50%) of the then outstanding common shares or voting power of such Party, other than acquisitions by employee benefit plans sponsored or maintained by such Party; (b) the consummation of a business combination involving such Party, unless, following such business combination, the stockholders of such Party immediately prior to such business combination beneficially own directly or indirectly more than fifty percent (50%) of the then outstanding common shares or voting power of the entity resulting from such business combination.

"***Change Overruns***" has the meaning set forth in Section 1.6.1(b).

"***CHDI***" means the CHDI Foundation, Inc.

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

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



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

"***Collaboration***" means the conduct of research and development of a Compound, Isis Development Candidate, or Brain Shuttle Development Candidate (as applicable), in each case in accordance with the applicable R&D Plan.

"***Collaboration Patents***" means collectively Roche Collaboration Patents, Isis Collaboration Patents and Jointly-Owned Collaboration Patents.

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

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

"***Commercially Reasonable Efforts***" means the carrying out of discovery, research, development or commercialization activities using good-faith commercially reasonable and diligent efforts that the applicable Party would reasonably devote to a compound or product of similar market potential or profit potential at a similar stage in development or product life resulting from its own research efforts, based on conditions then prevailing and taking into account, without limitation, issues of safety and efficacy, regulatory authority-approved labeling, product profile, the competitiveness of alternative products in the marketplace, the likely timing of the product's entry into the market, the patent and other proprietary position, the likelihood of approval and other relevant scientific, technical and commercial factors. The Isis Development Candidate-R&D Plan attached to this Agreement as of the Effective Date as APPENDIX 2 exemplifies a level of diligence that meets the Commercially Reasonable Efforts standard required under this Agreement. Without limiting any of the foregoing, (A) Commercially Reasonable Efforts as it applies to Roche's Development or Commercialization of a Product hereunder includes the use of Commercially Reasonable Efforts to (i) perform the Roche R&D Activities designated under the R&D Plans in accordance with the timelines set forth therein, (ii) perform the activities set forth in each IDCP in accordance with the timelines set forth therein, (iii) perform the "*General Activities*" set forth in APPENDIX 5, and (iv) achieve the specific performance milestone events set forth in APPENDIX 5 ("***Specific Performance Milestone Events***") for a Product on the timeline set forth in APPENDIX 5; *provided*, *however*, if (X) regulatory or Development issues arise that are outside of Roche's reasonable control and make achievement of any such Specific Performance Milestone Event on the stated timeline impossible, or (Y) an Isis Development Candidate is being Developed but Roche subsequently decides to Develop a Brain Shuttle Development Candidate in lieu of such Isis Development Candidate, the Parties will meet and negotiate in good faith to revise, consistent with any applicable Isis In-License Agreements, the date by which the applicable Specific Performance Milestone Event must be achieved; and (B) Commercially Reasonable Efforts as it applies to Isis' Development of a Product hereunder



includes use of Commercially Reasonable Efforts to perform the Isis R&D Activities designated under the R&D Plans in accordance with the timelines set forth therein. However, Roche (and its Affiliates) does not always seek to market its own products in every country or seek to obtain regulatory approval in every country or for every potential indication. As a result, the exercise of diligence by Roche is to be determined by judging Roche's commercially reasonable efforts in the Major Markets, taken as a whole.

"***Companion Diagnostic IP***" has the meaning set forth in Section 10.4.2(c).

"***Companion Diagnostic Product***" has the meaning set forth in Section 10.4.2(c).

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

"***Compound***" means an ASO that is designed to bind to (i) the RNA that encodes HTT (such ASO, a "***Non-Allele Selective Compound***"); or (ii) a SNP site within an HTT RNA that is associated with an expanded CAG repeat to selectively reduce the expanded CAG-repeat containing RNA relative to the normal

HTT RNA via an RNase H dependent mechanism (such ASO, an "***Allele Selective Compound***"), in each case where such ASO is discovered by Isis prior to or in the performance of an R&D Plan.

"***Compulsory Sublicense***" means a Sublicense granted to a Third Party, through the order, decree or grant of a governmental authority having competent jurisdiction, authorizing such Third Party to manufacture, use, sale, offer for sale, import or export a Product in any country.

"***Compulsory Sublicensee***" means a Third Party that was granted a Compulsory Sublicense.

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

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

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

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

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



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

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

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

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

"***Development Candidate***" means (i) a Brain Shuttle Development Candidate, or (ii) an Isis Development Candidate.

"***Development Candidate Data Package***" means, with respect to [***] the [***]; *provided* such package contains the [***]. The checklist Isis uses as of the Effective Date when reviewing potential development candidates for approval is attached hereto as APPENDIX 4.

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

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

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

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

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

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

"***Existing Diagnostic Agreement***" means that certain Non-Exclusive G-Clamp License Agreement between Isis and F. Hoffmann-La Roche Ltd dated April 26, 2011.

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

"***FDCA***" shall mean the United States Food, Drug and Cosmetics Act.

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

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

"***FTE***" means a total of forty-seven (47) weeks or one thousand eight hundred eighty (1,880) hours per year of work on the Development of a Product carried out by employees of a Party having the appropriate relevant expertise to conduct such activities.

"***FTE Rate***" means [***]. The FTE Rate will be prorated for the actual portion of the full year the employee works under this Agreement. The FTE Rate will be increased each Calendar Year after 2013 by the [***].

"***Full Royalty Period***" has the meaning set forth in Section 6.7.2(a).

"***Fully Absorbed Cost of Goods***" means the costs incurred by Isis as determined using the methodology set forth in SCHEDULE 1.7.1 fairly applied and as employed on a consistent basis throughout Isis' operations.

"***Generic Product***" means the product(s) of one or more Third Party that is not a Sublicensee, which has the same active pharmaceutical ingredient as a Product and for which in the U.S. an ANDA has been filed naming such Product as the reference listed drug or outside of the U.S., an equivalent process where bioequivalence to such Product has been asserted.

"***Group Sublicensee***" means any individual, corporation, association or other business entity:

**(i)** to which Roche has granted a Sublicense;

**(ii)** that is not an Affiliate of Roche; and

**(iii)** that is consolidated within Roche's externally published audited financial statements.

"***HSR Act***" means Section 7A of the Clayton Act, as added by Title II of the Hart-Scott-Rodino Antitrust Improvement Act of 1976, as amended, and the rules and regulations promulgated thereunder.

"***Huntingtin***" or "***HTT***" means the human gene known as IT15 or HD (GenBank accession #NM_002111.5), or any alternative splice variants, mutants, polymorphisms and fragments thereof.

"***Huntington's Disease***" or "***HD***" means the hereditary disorder caused by mutation associated with trinucleotide repeat expansion in the Huntingtin gene on chromosome 4p.

"***IDCP***" has the meaning set forth in Section 5.1.

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

"***IND-Enabling Toxicology Studies***" means the pre-clinical studies required to file an IND.



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

"***Independent Expert***" has the meaning set forth Section 5.1.1.

"***Initiation***" or "***Initiate***" means, (i) with respect to any IND-Enabling Toxicology Study, dosing of the first animal subject in such IND-Enabling Toxicology Study, (ii) with respect to any Clinical Study performed by Roche, its Affiliates or Sublicensees, the date the first patient is dosed with a Product in such Clinical Study, and (iii) with respect to any Clinical Study performed by Isis, its Affiliates or Sublicensees (excluding Roche), the date the first clinical trial site is approved by the applicable Reviewing Entity to participate in such Clinical Study.

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

"***Isis Collaboration Know-How***" means Know-How discovered, developed, invented or created solely by or on behalf of Isis or its Affiliate or a Third Party acting on their behalf in the performance of an R&D Plan, that is necessary or useful to Develop, Manufacture or Commercialize a Product in the Field.

"***Isis Collaboration Patents***" means Patent Rights discovered, developed, invented or created solely by or on behalf of Isis or its Affiliate or a Third Party acting on their behalf in the performance of an R&D Plan, that are necessary or useful to Develop, Manufacture or Commercialize a Product in the Field.

"***Isis Core Brain Shuttle Collaboration Patent***" has the meaning set forth in Section 7.2.2(a)(i).

"***Isis Core Technology Patents***" means all Patent Rights owned, used, developed by, or licensed to Isis or its Affiliates, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term, claiming subject matter generally applicable to ASOs, other than Isis Product-Specific Patents or Isis Manufacturing and Analytical Patents. A list of Isis Core Technology Patents as of the Effective Date is set forth on SCHEDULE 8.2.4(a) attached hereto.

"***Isis Development Candidate***" means a Compound that arises out of the Isis Development Candidate-R&D Plan that is reasonably determined by Isis' RMC in accordance with Isis' standard procedures for designating development candidates (and giving good faith consideration to the input of Roche's representatives on the JSC) as ready to start IND-Enabling Toxicology Studies. The checklist Isis uses as of the Effective Date when reviewing potential development candidates for approval is attached hereto as APPENDIX 4. The first Isis Development Candidate to be designated a Development Candidate

hereunder is referred to throughout this Agreement as the "*first*" Isis Development Candidate. Any work on one or more additional or replacement Isis Development Candidates may be performed under an amended Isis Development Candidate-R&D Plan as contemplated by Section 1.8.

"***Isis Development Candidate-R&D Plan***" means the research and development plan attached hereto as APPENDIX 2 (as may be amended in accordance with this Agreement) to conduct the Isis R&D Activities and Roche R&D Activities designated under such plan focused on the research and development of an Isis Development Candidate.

"***Isis Development Candidate Reverse Royalties***" has the meaning set forth in Section 6.10.1.

"***Isis In-License Agreements***" has the meaning set forth in Section 6.11.1(a).

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



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

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

"***Isis Manufacturing and Analytical Patents***" means Patent Rights, including Isis' interest in any Jointly-Owned Collaboration Patents, that claim methods and materials used in the synthesis or analysis of a Product regardless of sequence or chemical modification, owned, used, developed by, or licensed to Isis or its Affiliates, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term. A list of Isis Manufacturing and Analytical Patents as of the Effective Date is set forth on SCHEDULE 8.2.4(b) attached hereto. Isis Manufacturing and Analytical Patents do not include the Isis Product-Specific Patents or the Isis Core Technology Patents.

"***Isis Product-Specific Brain Shuttle Collaboration Patent***" has the meaning set forth in Section 7.2.2(a)(ii).

"***Isis Product-Specific Patents***" means Patent Rights Controlled by Isis or any of its Affiliates on or after the Effective Date claiming (i) the specific composition of matter of an Isis Development Candidate; (ii) methods of using an Isis Development Candidate as a prophylactic or therapeutic; or (iii) the specific mechanism of action of an Isis Development Candidate, in each case to the extent necessary to Develop, Manufacture or Commercialize an Isis Development Candidate; *provided however*, Patent Rights Controlled by Isis or any of its Affiliates that (y) include claims that are directed to subject matter applicable to ASOs in general, or (z) include an ASO, the sequence of which targets both (a) the RNA that encodes HTT and (b) ASOs that do not target the RNA encoding HTT, will not be considered Isis Product-Specific Patents, and in the case of (y) and (z), such Patent Rights will be considered Isis Core Technology Patents. A list of Isis Product-Specific Patents as of the Effective Date is set forth on SCHEDULE 8.2.4(c) attached hereto.

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

"***Isis Supported Pass-Through Costs***" means the licensing costs and payments payable by Isis to Third Parties to the extent arising from a Third Party agreement under [***].

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

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

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



"***Jointly-Owned Collaboration Know-How***" means Know-How discovered, developed, invented or created jointly in the performance of an R&D Plan by or on behalf of both Parties or their respective Affiliates or Third Parties acting on their behalf that is necessary or useful to Develop, Manufacture or Commercialize a Product in the Field.

"***Jointly-Owned Collaboration Patents***" means any Patent Rights discovered, developed, invented or created jointly in the performance of an R&D Plan by or on behalf of both Parties or their respective Affiliates or Third Parties acting on their behalf that is necessary or useful to Develop, Manufacture or Commercialize a Product in the Field.

"***Jointly-Owned Collaboration Technology***" means Jointly-Owned Collaboration Know-How and Jointly-Owned Collaboration Patents.

"***JSC***" has the meaning set forth in Section 1.5.1.

"***Know-How***" means unpatented inventions, technical information, know-how and materials, including technology, data, compositions, formulas, biological materials, assays, reagents, constructs, compounds, discoveries, procedures, processes, practices, protocols, methods, techniques, results of experimentation or testing, knowledge, trade secrets, skill and experience.

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

"***Licensed CMO***" has the meaning set forth in Section 4.1.4(a)(ii).

"***Licensed Know-How***" means Isis Manufacturing and Analytical Know-How, Isis Know-How, Isis Collaboration Know-How, and Isis' interest in any Jointly-Owned Collaboration Know-How. For clarity, Licensed Know-How does not include any Know-How covering formulation technology or delivery devices *unless* such Know-How is included in any Isis Collaboration Know-How or Jointly-Owned Collaboration Know-How.

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

"***Licensed Technology***" means any and all Licensed Patents and Licensed Know-How, in each case to the extent necessary or useful to Develop, Manufacture or Commercialize a Product. "*Licensed Technology*" expressly excludes all technology licensed to Isis under the UTSW Agreement because such technology is not utilized by, nor does it cover, the Compounds.

"***Linker-Specific Collaboration Patents***" has the meaning set forth in Section 7.1.3(a).

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

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

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



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

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

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

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

"***NAS Development Candidate***" has the meaning set forth in Section 2.1.1(b)(i).

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

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

"***Net Sales***" of a Product in a particular period will mean the amount calculated by subtracting from the Sales of such Product for such period: (A) a lump sum deduction of four percent (4%) of Sales under item (i) of the "*Sales*" definition in lieu of those deductions that are not accounted for on a Product-by-Product basis (e.g., freight, postage charges, transportation insurance, packing materials for dispatch of goods, custom duties); (B) uncollectible amounts accrued during such period based on a proportional allocation of the total bad debts accrued during such period; (C) credit card charges (including processing fees) accrued during such period on such Sales; and (D) government mandated fees and taxes and other government charges accrued during such period for such Product including, for example, any fees, taxes or other charges that become due in connection with any healthcare reform, change in government pricing or discounting schemes, or other action of a government or regulatory body; provided that the foregoing deductions under (A) to (D) were not already taken as a gross-to-net deduction in accordance with the then currently used International Financial Reporting Standards (IFRS) in the calculation of Sales of such Product for such period.

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

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

[***]

"***Omnibus Collaboration Patents***" has the meaning set forth in Section 7.1.3(a).

"***Option***" has the meaning set forth in Section 3.1.

"***Option Deadline***" has the meaning set forth in Section 3.1.

"***Option Period***" has the meaning set forth in Section 1.1.

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

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

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

"***Permitted Licenses***" means (1) licenses granted by Isis before or after the Effective Date to any Third Party under the Isis Core Technology Patents, the Isis Manufacturing and Analytical Patents, or the Isis Manufacturing and Analytical Know-How (but not under the Isis Product-Specific Patents) to (a) use oligonucleotides (or supply oligonucleotides to end users) solely to conduct pre-clinical research, or (b) enable such Third Party to manufacture or formulate oligonucleotides, where Isis does not assist such Third Party to identify, discover or make a Compound or Product; and (2) material transfer agreements with academic collaborators or non-profit institutions solely to conduct noncommercial research. A list of relevant Permitted Licenses as of the Effective Date is set forth on APPENDIX 7 attached hereto.

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

"***Phase 1 Trial***" means the initial clinical testing of a Product in humans (first-in-humans study) in any country that is designed to satisfy the requirements of 21 C.F.R. § 312.21(a) FDCA, as amended from time to time, or a foreign equivalent thereof.

"***Phase 1 Trial Data Package***" means the listing and tables of safety data (and early efficacy data if applicable) available to the Party conducting such Phase 1 Trial after the last patient receives his/her last dose of a Product in such Phase 1 Trial.

"***Phase 2 Trial***" means a human clinical study that is intended to explore a variety of dose and dose response to generate initial evidence of clinical safety and activity in a target patient population for which the primary endpoints include a determination of dose ranges and/or a preliminary determination of efficacy in patients being studied as described in 21 C.F.R. § 312.21(b) FDCA, as amended from time to time, or a foreign equivalent thereof.

"***Phase 2 Trial Data Package***" means, with respect to a given Phase 2 Trial, the listing and tables of safety and efficacy data available to Roche after the last patient has received his/her last dose of a Product in such Phase 2 Trial.

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

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

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



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

"***Prior Agreements***" means the agreements listed on SCHEDULE 8.2.7 attached hereto.

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

"***Product***" means a finished drug product containing as an active pharmaceutical ingredient (i) an Isis Development Candidate, or (ii) a Brain Shuttle Development Candidate.

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

"***R&D Plan***" means either (i) the Isis Development Candidate-R&D Plan, or (ii) the Brain Shuttle Development Candidate-R&D Plan.

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

"***Reduced Royalty Period***" has the meaning set forth in Section 6.7.2(d).

"***Reference Rate***" has the meaning set forth in Section 6.7.2(b).

"***Registration-Directed Trial***" means a pivotal Clinical Study (whether or not called a "*Phase 3*" Clinical Study) [***] intended to establish that a Product is safe and effective for its intended use; and is intended to support NDA filing (or foreign equivalent filing) of such Product in patients having the disease or condition being studied, as described in 21 C.F.R. § 312.21(c) FDCA, as amended from time to time, or a foreign equivalent thereof.

"***Registration-Directed Trial Data Package***" means, with respect to a given Registration-Directed Trial, the listing and tables of safety and efficacy data available [***].

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

"***Reviewing Entity***" means an institutional review board (IRB), research ethics board (REB), European ethical committee (EEC), or equivalent appropriate governmental ethical reviewing entity responsible for approving an entity to participate in a Clinical Study as a clinical site.

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

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

"***Roche Collaboration Know-How***" means Know-How discovered, developed, invented or created solely by or on behalf of Roche or its Affiliate or a Third Party acting on their behalf in the performance of an R&D Plan, that is necessary or useful to Develop, Manufacture or Commercialize a Product in the Field.

"***Roche Collaboration Patents***" means Patent Rights discovered, developed, invented or created solely by or on behalf of Roche or its Affiliate or a Third Party acting on their behalf in the performance of an R&D Plan, that are necessary or useful to Develop, Manufacture or Commercialize a Product in the Field.



"***Roche Collaboration Technology***" means Roche Collaboration Know-How, Roche Collaboration Patents and Roche's interest in any Jointly-Owned Collaboration Technology and Brain Shuttle Collaboration Patents.

"***Roche Existing Brain Shuttle Patents***" has the meaning set forth in Section 8.4.1. A list of Roche Existing Brain Shuttle Patents as of the Effective Date is set forth on SCHEDULE 8.4.1 attached hereto.

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

"***Roche Know-How***" means any Know-How that (i) did not arise in connection with the performance of an R&D Plan, (ii) is owned, used, developed by, or licensed to Roche or its Affiliates, and (iii) is necessary or useful to Develop, Manufacture or Commercialize a Product in the Field, in each case to the extent Controlled by Roche or its Affiliates on the Effective Date or at any time during the Agreement Term.

"***Roche Patents***" means any Patent Rights that (i) did not arise in connection with the performance of an R&D Plan, (ii) are owned, used, developed by, or licensed to Roche or its Affiliates, and (iii) are necessary or useful to Develop, Manufacture or Commercialize a Product in the Field, in each case to the extent Controlled by Roche or its Affiliates on the Effective Date or at any time during the Agreement Term.

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

"***Roche Reduced Royalty***" has the meaning set forth in Section 6.7.2(b).

"***Roche R&D Activities***" means the research, pre-clinical and/or clinical activities for which Roche is designated as responsible under an R&D Plan.

"***Roche Supported Pass-Through Costs***" means the [***].

"***Roche-Selected Brain Shuttle Development Candidate***" means that as between a given Isis Development Candidate and a given Brain Shuttle Development Candidate, in accordance with Section 5.1.1, the Independent Expert did not recommend that such Brain Shuttle Development Candidate be progressed into Phase 2 Trials.

"***Roche Technology***" means Roche's interest in Roche Collaboration Technology, Roche Know-How, Roche Patents and any trademarks described in Section 4.1.7, owned, used, developed by, or licensed to Roche or its Affiliates that is necessary or useful to Develop, Manufacture or Commercialize a Product.

"***Royalty Quotient***" has the meaning set forth in Section 6.7.2(b).

"***Sales***" of a Product in a particular period will mean the sum of (i) and (ii):

**(i)** the amount stated in Roche sales line of its externally published audited financial statements with respect to such Product for such period (excluding sales to any Sublicensee that are used for research or Development or re-sold by such Sublicensee as sales under item (ii) below). This amount reflects the gross invoice price at which such Product was sold or otherwise disposed of (other than for use as clinical supplies or free samples) by Roche/Genentech, its Affiliates and Group Sublicensees to Third Parties



(excluding sales to any Sublicensee that are used for research or Development or re-sold by such Sublicensee as sales under item (ii) below) in such period reduced by gross-to-net deductions, if not previously deducted from such invoiced amount, taken in accordance with the then currently used International Financial Reporting Standards (IFRS).

By way of example, the gross-to-net deductions taken in accordance with International Financial Reporting Standards (IFRS) as of the Effective Date include the following:

(a) credits, reserves or allowances granted for (w) damaged, outdated, returned, rejected, withdrawn or recalled Product, (x) wastage replacement and short-shipments, (y) billing errors and (z) indigent patient and similar programs (e.g., price capitation);

(b) governmental price reductions and government mandated rebates;

(c) chargebacks, including those granted to wholesalers, buying groups and retailers;

(d) customer rebates, including cash sales incentives for prompt payment, cash and volume discounts; and

(e) taxes, duties and any other governmental charges or levies imposed upon or measured by the import, export, use, manufacture or sale of a Product (excluding income or franchise taxes).

For the purpose of clarity, sales by Roche/Genentech and its Affiliates to any Sublicensee and/or Group Sublicensee that are used for research or Development or re-sold by such Sublicensee or Group Sublicensee as sales under item (ii) below will be excluded from "*Sales*" calculated under this item (i).

**(ii)** Sublicensee (excluding Compulsory Sublicensee) sales amounts reported to Roche and its Affiliates in accordance with Sublicensee contractual terms and their then currently used accounting standards. For the purpose of clarity, any Sublicensee sales as reported to Roche in accordance with Compulsory Sublicense agreements will be excluded from the Sales amount.

"***SNP***" means single nucleotide polymorphism.

"***Specific Performance Milestone Event***" has the meaning set forth in the definition of "*Commercially Reasonable Efforts*."

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

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

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

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



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

"***UTSW Agreement***" means that certain Exclusive Patent License Agreement between Isis and the University of Texas Southwestern Medical Center at Dallas dated June 24, 2010.

"***Valid Claim***" means a claim (i) of any issued, unexpired United States or foreign Patent Right, which will not, in the country of issuance, have been donated to the public, disclaimed, nor held invalid or unenforceable by a court of competent jurisdiction in an unappealed or unappealable decision, or (ii) of any United States or foreign patent application within a Patent Right, which will not, in the country in question, have been cancelled, withdrawn, abandoned nor been pending for more than seven (7) years, not including in calculating such seven-year period of time in which such application is in interference or opposition or similar proceedings or time in which a decision of an examiner is being appealed. Notwithstanding the foregoing, on a country-by-country basis, a patent application pending for more than seven years will not be considered to have any Valid Claim for purposes of this Agreement unless and until a patent meeting the criteria set forth in clause (i) above with respect to such application issues.



## APPENDIX 2

**Isis Development Candidate-R&D Plan**

[***]



## APPENDIX 3

**Brain Shuttle Development Candidate-R&D Plan**

[***]



## APPENDIX 4

**Isis Development Candidate Checklist**

[***]

**APPENDIX 5**

**Roche's Development and Commercialization Activities and Specific Performance Milestone Events**

**[***]**



**APPENDIX 6**

**Brain Shuttle Collaboration Patents**

**[To be added/updated during Agreement Term]**



**APPENDIX 7**

**Relevant Permitted Licenses as of the Effective Date**

**[***]**



**SCHEDULE 1.5.1**

**JSC GOVERNANCE**

**(a)** One of the primary purposes of the JSC is to empower the JSC to make decisions with respect to the composition and conduct of the R&D Plans that are not specifically vested in a Party under this Agreement. Nothing in this SCHEDULE 1.5.1 is intended to affect any decision-making authority granted to a Party in the body of the Agreement.

**(b)** The JSC will begin on the Effective Date and will dissolve upon the first Approval; *provided, however*, that Isis' obligation to participate in the JSC will terminate upon Option exercise. Thereafter, Isis will have the right, but not the obligation, to participate in JSC meetings.

**(c)** The JSC will determine the JSC operating procedures, including frequency of meetings (at least quarterly prior to Option exercise and at least yearly after Option exercise), location of meetings, and responsibilities for agendas and minutes. The JSC will codify these operating procedures in the written minutes of the first meeting.

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

**(e)** The chairperson will be responsible for ensuring that activities occur as set forth in this Agreement, including ensuring that JSC meetings occur, JSC recommendations are properly reflected in the minutes, and any dispute is given prompt attention and resolved in accordance with Section 1.5.2, Section 7.1.3 and Section 12.1, as applicable.

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

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

**(h)** Without limiting the provisions of Section 1.5.1, subject to Section 1.5.2, the JSC will perform the following functions:

(i) advise on the details and deliverables for the selection of Development Candidates;

(ii) review the overall progress of efforts to select Development Candidates;

(iii) review emerging data and consider changes to the R&D Plans;

(iv) review, provide advice and recommend revisions to the R&D Plans

(v) discuss the selection of the Brain Shuttle Development Candidate;

(vi) materially amend the R&D Plans upon the JSC's unanimous written consent;

(vii) record recommendations and decisions of the JSC in the JSC's meeting minutes;

(viii) such other review and advisory responsibilities assigned to the JSC pursuant to this Agreement; and

(ix) discuss whether to continue with Change Overruns.



**SCHEDULE 1.5.3**

**Alliance Management Activities**

Each Alliance Manager is responsible for:

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

**(b)** Developing a mutually agreed alliance launch plan covering any activities and systems that the Parties need to implement within the first one hundred (100) days after the Effective Date to support the R&D Plans;

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

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

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

**(f)** Ensuring compliance in maintaining the Isis Internal ASO Safety Database as outlined in Section 5.2.2;

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

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



**SCHEDULE 1.6.2(b)(i)**

**Cost of ASOs Supplied Under the Brain Shuttle Development Candidate-R&D Plan**

**[***]**



**SCHEDULE 1.7.1**

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

[***]



**SCHEDULE 6.7.2(e)**

**Royalty Calculation Examples**

[***]

**SCHEDULE 6.7.2(f)**

**Allocation of Net Sales**

[***]



**SCHEDULE 6.11.1**

**Isis In-License Agreements**

**(Relevant to Compounds as of the Effective Date)**

[***]



**SCHEDULE 8.2.4(a)**

**Isis Core Technology Patents**

[***]



**SCHEDULE 8.2.4(b)**

**Isis Manufacturing and Analytical Patents**

[***]



**SCHEDULE 8.2.4(c)**

**Isis Product-Specific Patents**

[***]

**SCHEDULE 8.2.7**

**Prior Agreements**

[***]

**SCHEDULE 8.4.1**

**Roche Existing Brain Shuttle Patents**

[***]

**EXHIBIT 10.2**

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

April 8, 2013

CHDI Foundation, Inc.
c/o CHDI Management, Inc.
350 Seventh Avenue, Suite 601
New York, NY 10001

Attention: Robi Blumenstein, President

**Re:** Research Agreement dated August 10, 2011 (the "***Agreement***") between Isis Pharmaceuticals, Inc. ("***Isis***") and CHDI Foundation, Inc. (the "***Foundation***")

To whom it may concern:

This letter agreement serves to confirm certain additional agreements between Isis and the Foundation related to the Agreement and the subject matter thereof.

Isis and the Foundation agree as follows:

1. Definitions.

    a. Terms which are defined in the Agreement shall bear the same definitions in this letter agreement.

    b. Capitalized terms in this letter agreement followed by the designation "(def. RCA)" shall bear the same definition as in the HTT Research, Development, Option and License Agreement between Isis and F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc. (or any of their Affiliates, "***Roche***") related to Isis' Huntington's Disease program (the "***Roche Collaboration Agreement***"), a copy of which is attached hereto.

    c. Unless otherwise defined in this letter agreement, the following terms have the meanings set forth below:

        i. "***Best Estimate All-In Preclinical Costs***" means, on any date, the sum of (X) all costs and expenses actually incurred by Isis on or prior to that date in performing its obligations under Section 1.6.1(a) of the Roche Collaboration Agreement, and (Y) Isis' good faith estimate of the additional costs and expenses to be incurred by Isis to complete the then-current Isis Development Candidate-R&D Plan (def. RCA). It is agreed that for the purpose of this calculation, costs and expenses will be estimated and determined on the same basis as that used for the Roche Collaboration Agreement and Isis will provide the Foundation with details of such calculation.

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        ii. "***Commercialization***" means activities directed to marketing, promoting, or selling a Project Compound.

        iii. "***Develop***" or "***Development***" means human clinical trials and other development activities reasonably related to supporting the approval of a Project Compound by a regulatory authority.

        iv. "***Isis Max Amount***" means, on any date, the greater of (X) [***] and (Y) [***] on that date.

        v. "***MAD Trial***" means a multiple ascending dose Phase 1 Trial (def. RCA) of a finished drug product containing an Isis Development Candidate (def. RCA) as the active pharmaceutical ingredient.

        vi. "***SAD Trial***" means a single ascending dose Phase 1 Trial (def. RCA) of a finished drug product containing an Isis Development Candidate (def. RCA) as the active pharmaceutical ingredient.

2. Consent. Notwithstanding the terms of the Agreement but on and subject to the terms and conditions set forth in this letter agreement, the Foundation consents to Isis entering into and performing (including granting the license set forth in Section 4.1.1 thereof) the Roche Collaboration Agreement.

3. Foundation's License Grant to Isis; Foundation's Retained License Rights; Indemnity.

    a. For the sole purpose of enabling Isis to sublicense the Foundation's interest in, to and under the Project HD Intellectual Property and Project Compounds that are the subject of the Roche Collaboration Agreement, the Foundation hereby grants to Isis a fully-paid up, royalty-free, license (with the limited right to grant a sublicense pursuant to the Roche Collaboration Agreement) to the Foundation's interest in, to and under such Project HD Intellectual Property and Project Compounds, having the same scope as the license Isis is granting to Roche under the Roche Collaboration Agreement; *provided*, *however*, that the Foundation retains the rights reserved by the Foundation under Section 10(a)(ii) of the Agreement in respect of all Project HD Intellectual Property and any Project Compound.

    b. During the term of any Option (def. RCA), the Foundation will not Develop (on its own or with a Third Party) any Project Compounds that are licensed to Roche under the Roche Collaboration Agreement ([***]).

    c. So long as Isis and/or Roche is developing or commercializing an ASO designed to bind to the RNA that encodes Huntington under the Roche Collaboration Agreement, the Foundation will not Develop or Commercialize (on its own or with a Third Party) any Project Compound.

    d. Isis will defend and indemnify the Foundation Indemnified Parties against any and all costs, damages, expenses (including reasonable legal fees) and losses suffered by any Foundation Indemnified Party in connection with any Third Party action, assessment,

claim, demand, proceeding or suit to the extent arising or resulting from the Roche Collaboration Agreement. The indemnity procedures set forth in Section 20(e) of the Agreement will apply to any indemnity claims made by a Foundation Indemnified Party under this paragraph 3(d).

4. Foundation Participation in JSC. During the term of the joint steering committee ("***JSC***") under the Roche Collaboration Agreement, the Foundation will have the right to appoint a non-voting observer to participate in JSC meetings; *provided*, *however*, if Isis and Roche reasonably determine in good faith after discussion with the Foundation that, due to participation in programs with a potentially competitive drug, the Foundation observer should no longer participate in JSC meetings and be exposed to program data, Isis will provide the Foundation with written notice of such determination and thereafter the Foundation observer will no longer participate in meetings of the JSC. The Foundation observer shall be a person reasonably acceptable to both Roche and Isis.

5. Financial Provisions.

   a. Notwithstanding anything else contained in the Agreement, the Foundation shall not be obligated to make any payments to Isis under the Agreement for work performed by Isis under the Agreement after [***].

   b. Within five (5) days following the receipt by Isis of the fee described in Section 6.1 of the Roche Collaboration Agreement, Isis will pay the Foundation the sum of one million five hundred thousand dollars (US$1,500,000).

   c. Within five (5) days following the designation by Isis of an Isis Development Candidate (def. RCA) pursuant to Section 1.2.3(a) of the Roche Collaboration Agreement, Isis will pay the Foundation the sum of one million five hundred thousand dollars ($1,500,000).

   d. Within five (5) days following the receipt by Isis of the [***] pursuant to Section 6.2 of the Roche Collaboration Agreement, Isis will pay the Foundation an amount equal to the lesser of (i) [***], and (ii) the Isis Max Amount on the date of payment less the aggregate of all amounts previously paid to the Foundation pursuant to this Section 5 as of such date.

   e. Within five (5) days after the [***], Isis will pay the Foundation an amount equal to the lesser of (i) [***] pursuant to this Section 5, and (ii) the Isis Max Amount on the date of payment less the aggregate of all amounts previously paid to the Foundation pursuant to this Section 5 as of such date.

   f. Within five (5) days after the [***], Isis will pay the Foundation an amount equal to the lesser of (i) [***] pursuant to this Section 5, and (ii) the Isis Max Amount on the date of payment less any amounts previously paid to the Foundation pursuant to this Section 5.



   g. All payments made by Isis to the Foundation pursuant to this letter agreement will be deemed to be payments by Isis in satisfaction of its obligations under Section 13 of the Agreement and, notwithstanding any provision to the contrary in this letter agreement, Isis will not be obligated to pay the Foundation an aggregate amount in excess of the total sum payable by Isis to the Foundation under Section 13 of the Agreement.

   h. The balance of the amount payable to the Foundation under Section 13 of the Agreement will be deemed to be due and payable five (5) days following the receipt by Isis of any license fee described in Section 6.3 of the Roche Collaboration Agreement and Isis.

   i. Upon the payment in full by Isis of the amount due to the Foundation under Section 13 of the Agreement, (i) the Agreement will be deemed to be terminated by mutual agreement of the Parties in accordance with Section 17(a) of the Agreement, and (ii) Isis will be under no further obligation to deliver Isis Provided Documents pursuant to Section 6(d) of this letter agreement.

6. Isis Covenants.

   a. Isis will use commercially reasonable efforts to promptly (i) exercise the rights granted to Isis under the Roche Collaboration Agreement, (ii) discharge the obligations of Isis under the Roche Collaboration Agreement and (iii) cause Roche to fulfill its obligations under the Roche Collaboration Agreement, in each case to the extent necessary to cause Roche to use good-faith commercially reasonable and diligent efforts to maintain a program of ongoing research, development and commercialization of the lead Project Compound for Huntington's disease;

   b. Isis will not, without the Foundation's prior written consent, amend or waive any term or provision of the Roche Collaboration Agreement if such amendment or waiver would materially affect or alter the obligation of Isis or Roche to use good-faith commercially reasonable and diligent efforts to maintain a program of ongoing research, development and commercialization of the lead Project Compound for Huntington's disease;

   c. Isis will not, without the Foundation's prior written consent, consent to any request by, or any action or omission of, Roche if such consent would materially affect or alter the obligation of Isis or Roche to use good-faith commercially reasonable and diligent efforts to maintain a program of ongoing research, development and commercialization of the lead Project Compound for Huntington's disease;

   d. Isis will, within a reasonable period of time following the delivery of any report or analysis required to be delivered by it pursuant to Section 1.4 of the Roche Collaboration Agreement (each, an "***Isis Provided Document***"), deliver a complete and correct copy of each such Isis Provided Document to the Foundation; and

   e. Isis and the Foundation agree that the Isis Provided Documents shall be deemed Isis Confidential Information and shall be treated by Isis and the Foundation in accordance with Section 14 of the Agreement; *provided*, *that*, the Foundation shall have the right to use the Isis Provided

Documents for all uses and purposes to the extent necessary or useful to enable the Foundation to perform its obligations or exercise its rights under this letter agreement.



7. Termination of Roche Collaboration Agreement. If the Roche Collaboration Agreement is terminated or expires for any reason, without further action of Isis or the Foundation, the following will automatically occur:

    a. the license granted by the Foundation to Isis in paragraph 3 of this letter agreement will terminate;

    b. the sublicense granted by Isis to Roche under the Roche Collaboration Agreement to the Foundation's interest in, to and under the Project HD Intellectual Property and Project Compounds will terminate;

    c. the obligations of Isis and the Foundation under paragraph 6(a) through (e) of this letter agreement will terminate; and

    d. subject to the terms of this letter agreement, each of Isis' and the Foundation's rights in and to the Project HD Intellectual Property and Project Compounds licensed under the Roche Collaboration Agreement will automatically revert back to the rights each Party had immediately prior to the date of this letter agreement (giving due credit to any amounts previously paid by Isis to the Foundation hereunder).

8. Idem. If the Roche Collaboration Agreement is terminated or expires for any reason prior to [***], Isis will pay the Foundation an amount equal to (a) one-half of (i) [***] minus (ii) all costs and expenses actually incurred by Isis on or prior to the date of such termination or expiration in performing its obligations under Section 1.6.1(a) of the Roche Collaboration Agreement, minus (b) any amounts previously paid to the Foundation pursuant to Section 5 of this letter agreement.

9. Incorporation by Reference. Section 14 and Sections 18 through 29 of the Agreement, inclusive, are incorporated into this letter agreement by reference.

10. Replacement of Earlier Agreement. This letter agreement supersedes and replaces the letter agreement dated August 10, 2011 between Isis and the Foundation.

11. Further Assurances. The Foundation will, at Isis' expense, (a) execute such further documents, instruments, licenses and assurances and (b) take such further actions, in each case as Isis may reasonably request to give effect to this letter and the Roche Collaboration Agreement; *provided, that*, such further documents, instruments, licenses, assurances and actions will not amend or modify in any way (i) either Isis' or the Foundation's rights or obligations under this letter agreement or (ii) either Isis' or Roche's rights or obligations under the Roche Collaboration Agreement.

Except as otherwise expressly amended by this letter agreement, the terms of the Agreement remain in full force and effect in accordance with its terms.



By signing where indicated below, as of the date of this letter agreement, Isis and the Foundation indicate their acceptance and agreement to the foregoing terms and conditions.

Best regards,

**ISIS PHARMACEUTICALS, INC.**

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

Acknowledged and Agreed:

**CHDI FOUNDATION, INC.**

By: /s/ *Robi Blumenstein*
CHDI Management, Inc., as authorized agent of
CHDI Foundation, Inc.
By: Robi Blumenstein, President — CHDI Management, Inc.

**EXHIBIT 31.1**

**CERTIFICATION**

I, Stanley T. Crooke, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: August 6, 2013

/s/ Stanley T. Crooke

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

**EXHIBIT 31.2**

**CERTIFICATION**

I, Elizabeth L. Hougen, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: August 6, 2013

/s/ Elizabeth L. Hougen

Elizabeth L. Hougen
*Chief Financial Officer*

**Exhibit 32.1**

**CERTIFICATION**

Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, Stanley T. Crooke, the Chief Executive Officer of Isis Pharmaceuticals, Inc., (the "Company"), and Elizabeth L. Hougen, the Chief Financial Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

1. The Company's Quarterly Report on Form 10-Q for the period ended June 30, 2013, to which this Certification is attached as Exhibit 32.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

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

Dated: August 6, 2013

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

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