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 March 31, 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 May 2, 2013 was 103,780,421.

ISIS PHARMACEUTICALS, INC.
FORM 10-Q
INDEX

TRADEMARKS

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

Regulus Therapeutics™ is a trademark of Regulus Therapeutics Inc.

KYNAMRO™ is a trademark of Genzyme Corporation

Juxtapid™ is a trademark of Aegerion Pharmaceuticals, Inc.

Table of Contents

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

	March 31, 2013 (Unaudited)	December 31, 2012
ASSETS		
Current assets:		
Cash and cash equivalents	$ 107,650	$ 124,482
Short-term investments	264,261	249,964
Contracts receivable	1,172	522
Inventories	5,809	6,121
Investment in Regulus Therapeutics Inc.	44,863	33,622

Other current assets	8,074	8,727
Total current assets	431,829	423,438
Property, plant and equipment, net	89,694	91,084
Licenses, net	6,010	6,579
Patents, net	19,604	18,646
Deposits and other assets	5,824	5,939
Total assets	$ 552,961	$ 545,686
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 5,385	$ 10,239
Accrued compensation	3,818	7,878
Accrued liabilities	17,758	15,401
Accrued income taxes	3,582	—
Current portion of long-term obligations	4,508	4,879
Current portion of deferred contract revenue	35,244	35,925
Total current liabilities	70,295	74,322
Long-term deferred contract revenue	58,816	66,656
2 3/4 percent convertible senior notes	145,533	143,990
Long-term obligations, less current portion	6,498	7,402
Long-term financing liability for leased facility	70,728	70,550
Total liabilities	351,870	362,920
Stockholders' equity:		
Common stock, $0.001 par value; 200,000,000 shares authorized, 102,695,200 and 101,481,134 shares issued and outstanding at March 31, 2013 and December 31, 2012, respectively	103	102
Additional paid-in capital	1,091,842	1,077,150
Accumulated other comprehensive gain	17,784	12,480
Accumulated deficit	(908,638)	(906,966)
Total stockholders' equity	201,091	182,766
Total liabilities and stockholders' equity	$ 552,961	$ 545,686

See accompanying notes.

Table of Contents

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

	Three Months Ended March 31,	
	2013	2012
Revenue:		
Research and development revenue under collaborative agreements	$ 41,921	$ 21,818
Licensing and royalty revenue	1,439	1,417
Total revenue	43,360	23,235
Expenses:		
Research and development	38,312	38,714
General and administrative	3,423	2,976
Total operating expenses	41,735	41,690
Income (loss) from operations	1,625	(18,455)
Other income (expense):		
Equity in net loss of Regulus Therapeutics Inc.	—	(976)
Investment income	376	600
Interest expense	(4,795)	(5,179)
Gain on investments, net	1,058	17
Loss before income tax benefit (expense)	(1,736)	(23,993)
Income tax benefit (expense)	64	(2)
Net loss	$ (1,672)	$ (23,995)
Basic and diluted net loss per share	$ (0.02)	$ (0.24)
Shares used in computing basic and diluted net loss per share	101,875	100,157

See accompanying notes.

Table of Contents

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

	Three Months Ended March 31,	
	2013	2012
Net loss	$ (1,672)	$ (23,995)
Unrealized gains on securities, net of tax	6,467	528
Reclassification adjustment for realized gain on the sale of Sarepta shares included in net loss	(1,163)	—
Comprehensive income (loss)	$ 3,632	$ (23,467)

See accompanying notes.

Table of Contents

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

	Three Months Ended March 31,	
	2013	2012
Net cash used in operating activities	$ (10,576)	$ (6,711)
Investing activities:		
Purchases of short-term investments	(64,552)	(61,841)
Proceeds from the sale of short-term investments	49,076	61,781
Purchases of property, plant and equipment	(222)	(113)
Acquisition of licenses and other assets, net	(702)	(349)
Proceeds from sale of strategic investments	1,094	—
Net cash used in investing activities	(15,306)	(522)
Financing activities:		
Proceeds from issuance of equity	11,823	638
Principal payments on debt and capital lease obligations	(2,773)	(2,491)
Net cash provided by (used in) financing activities	9,050	(1,853)
Net decrease in cash and cash equivalents	(16,832)	(9,086)
Cash and cash equivalents at beginning of period	124,482	65,477
Cash and cash equivalents at end of period	$ 107,650	$ 56,391
Supplemental disclosures of cash flow information:		
Interest paid	$ 113	$ 2,211
Income taxes paid	$ 2	$ —
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 715	$ 844

See accompanying notes.

Table of Contents

ISIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
March 31, 2013
(Unaudited)

1. Basis of Presentation

The unaudited interim condensed consolidated financial statements for the three month periods ended March 31, 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 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 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 and are eligible to receive a $6 million payment in the second quarter of 2013 assuming the research program is continuing. We are also eligible to receive milestone payments, license fees for the research program targets and royalties on any product sales of drugs resulting from this collaboration. In exchange, we granted AstraZeneca an exclusive license to develop and commercialize ISIS-STAT3$_{Rx}$ and ISIS-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-AZ1$_{Rx}$. AstraZeneca will be responsible for all other global development, regulatory and commercialization activities for ISIS-STAT3$_{Rx}$ and ISIS-AZ1$_{Rx}$. 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

Table of Contents

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 will perform for ISIS-STAT3$_{Rx}$;
- The exclusive license we granted to AstraZeneca to develop and commercialize ISIS-AZ1$_{Rx}$ and the research services we will perform for ISIS-AZ1$_{Rx}$; 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 revenue allocated to the ISIS-STAT3$_{Rx}$ license on the date of the agreement because that is when we delivered the license. We will recognize the revenue allocated to the development services for ISIS-STAT3$_{Rx}$ over the period of time we perform services. The ISIS-AZ1$_{Rx}$ license is also an exclusive license. Because of the early stage of research for ISIS-AZ1$_{Rx}$, we believe that our knowledge and expertise with antisense technology is essential for AstraZeneca or another third party to successfully develop ISIS-AZ1$_{Rx}$. As a result, we concluded that the ISIS-AZ1$_{Rx}$ license does not have stand-alone value and we combined the ISIS-AZ1$_{Rx}$ license and related research services into one unit of accounting. We will recognize 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 will recognize revenue for the combined unit of accounting over the period of our performance.

We determined that the 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. 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 $25 million upfront payment based on the relative BESP of each unit of accounting. We engaged a third party, independent valuation expert to assist us with determining BESP. We estimated the selling price of the licenses granted for ISIS-STAT3$_{Rx}$ and ISIS-AZ1$_{Rx}$ 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 $25 million upfront payment in December 2012 for the ISIS-STAT3$_{Rx}$ license. We are recognizing the remaining $15.7 million over the estimated period of our performance. Assuming a constant selling price for the other elements in the arrangement, if there was an assumed ten percent increase or decrease in the estimated selling price of the ISIS-STAT3$_{Rx}$ license, we determined that the revenue we would have allocated to the ISIS-STAT3$_{Rx}$ license would change by approximately seven percent, or $600,000, from the amount we recorded.

Table of Contents

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

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

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 are yet to be defined, 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 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

Table of Contents

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:

- 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;

Table of Contents

- 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. In the first quarter of 2013, the FDA approved the NDA for KYNAMRO and we initiated a Phase 2/3 clinical study for ISIS-TTR$_{Rx}$, the first drug selected as part of our collaboration with GSK. We consider milestones 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, in the first quarter of 2013 we recognized the $25 million milestone payment from Genzyme and the $7.5 million milestone payment from GSK. Further information about our collaborative arrangements can be found in Note 7 *Collaborative Arrangements and Licensing Agreements* and Note 7 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 March 31, 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. Most of 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 three months of 2013 and 2012. Total inventory, which consisted of raw materials, was $5.8 million and $6.1 million as of March 31, 2013 and December 31, 2012, respectively.

Table of Contents

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.

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 loss for the three months ended March 31, 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:

- 2¾ percent convertible senior notes;
- 2⅝ percent convertible subordinated notes;
- GlaxoSmithKline convertible promissory notes issued by Regulus;
- Dilutive stock options; and
- Restricted stock units.

We redeemed all of our 2⅝ 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 2⅝ percent notes and GSK convertible promissory notes are not common equivalent shares for the three months ended March 31, 2013.

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 March 31, 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 March 31, 2013, the total carrying value of our investments in variable interest entities was $47.5 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.

Table of Contents

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 months ended March 31, 2013 and 2012 (in thousands):

	Three Months Ended March 31,	
	2013	2012
Beginning balance accumulated other comprehensive income (loss)	$ 12,480	$ (770)
Other comprehensive income before reclassifications, net of tax (1)	6,467	528
Amounts reclassified from accumulated other comprehensive income (2)	(1,163)	—
Net current period other comprehensive income	5,304	528
Ending balance accumulated other comprehensive income (loss)	$ 17,784	$ (242)

(1) Other comprehensive income for the three months ended March 31, 2013 includes income tax expense of $3.6 million.

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

Convertible debt

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

Segment information

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

Stock-based compensation expense

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

Table of Contents

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 three months ended March 31, 2013 and 2012, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Three Months Ended March 31,	
	2013	2012
Risk-free interest rate	1.0%	1.1%
Dividend yield	0.0%	0.0%
Volatility	51.5%	50.6%
Expected life	5.1 years	5.1 years

ESPP:

	Three Months Ended March 31,	
	2013	2012
Risk-free interest rate	0.1%	0.1%
Dividend yield	0.0%	0.0%
Volatility	61.4%	43.4%
Expected life	6 months	6 months

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 three months ended March 31, 2013 and 2012 was $14.21 and $7.60, respectively.

The following table summarizes stock-based compensation expense for the three months ended March 31, 2013 and 2012 (in thousands), which was allocated as follows:

	Three Months Ended March 31,	
	2013	2012
Research and development	$ 2,546	$ 1,935
General and administrative	323	332
Total	$ 2,869	$ 2,267

As of March 31, 2013, total unrecognized estimated non-cash stock-based compensation expense related to non-vested stock options and RSUs was $10.7 million and $3.8 million, respectively. We will adjust total unrecognized compensation cost for future changes in estimated forfeitures. We expect to recognize the cost of non-cash, stock-based compensation expense related to non-vested stock options and RSUs over a weighted average amortization period of 1.4 years and 2.1 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 March 31, 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.

Table of Contents

The following table summarizes the contract maturity of the available-for-sale securities we held as of March 31, 2013:

One year or less	47%
After one year but within two years	41%
After two years but within three years	12%
Total	100%

As illustrated above, we primarily invest our excess cash in short-term instruments with 88 percent of our available-for-sale securities having a maturity of less than two years.

At March 31, 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):

March 31, 2013	Amortized Cost	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Short-term investments:					
Corporate debt securities	$ 97,983	$ 59	$ (29)	$ —	$ 98,013
Debt securities issued by U.S. government agencies	9,932	1	(46)	—	9,887
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	15,549	55	(11)	—	15,593
Total securities with a maturity of one year or less	124,464	116	(86)	—	124,494
Corporate debt securities	107,131	110	(156)	—	107,085
Debt securities issued by U.S. government agencies	15,020	35	(3)	—	15,052
Debt securities issued by the U.S. Treasury	12,393	30	—	—	12,423
Debt securities issued by states of the United States and political subdivisions of the states	5,203	7	(3)	—	5,207
Total securities with a maturity of more than one year	139,747	182	(162)	—	139,767
Subtotal	$ 264,211	$ 298	$ (248)	$ —	$ 264,261

March 31, 2013	Cost Basis	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Equity securities:					
Current portion (Regulus Therapeutics Inc.)	$ 15,525	$ 29,338	$ —	$ —	$ 44,863
Current portion (included in Other current assets)	1,538	1,961	—	(880)	2,619
Long-term portion (included in Deposits and other assets)	625	—	—	—	625
Subtotal	$ 17,688	$ 31,299	$ —	$ (880)	$ 48,107
	$ 281,899	$ 31,597	$ (248)	$ (880)	$ 312,368

Table of Contents

December 31, 2012	Amortized Cost	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Short-term investments:					
Corporate debt securities	$ 113,249	$ 81	$ (9)	$ —	$ 113,321
Debt securities issued by U.S. government agencies	10,100	2	(66)	—	10,036
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	140,909	102	(77)	—	140,934
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
Subtotal	$ 249,839	$ 310	$ (185)	$ —	$ 249,964

	Cost	Unrealized		Other-Than-Temporary Impairment	Estimated

December 31, 2012	Basis	Gains	Losses	Loss	Fair Value
Equity securities:					
Current portion (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
Subtotal	$ 17,730	$ 22,271	$ —	$ (880)	$ 39,121
	$ 267,569	$ 22,581	$ (185)	$ (880)	$ 289,085

Investments we considered to be temporarily impaired at March 31, 2013 were as follows (in thousands):

		Less than 12 months of temporary impairment	
	Number of Investments	Estimated Fair Value	Unrealized Losses
Corporate debt securities	70	$ 95,606	$ (185)
Debt securities issued by U.S. government agencies	4	13,885	(49)
Debt securities issued by states of the United States and political subdivisions of the states	3	4,537	(14)
Total temporarily impaired securities	77	$ 114,028	$ (248)

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.

Table of Contents

4. Fair Value Measurements

We use a three-tier fair value hierarchy to prioritize the inputs used in our fair value measurements. These tiers include: Level 1, defined as observable inputs such as quoted prices in active markets for identical assets, which includes our money market funds and treasury securities classified as available-for-sale securities and an investment in equity securities in a publicly-held biotechnology company; Level 2, defined as inputs other than quoted prices in active markets that are either directly or indirectly observable, which includes our fixed income securities and commercial paper classified as available-for-sale securities; and Level 3, defined as unobservable inputs in which little or no market data exists, therefore requiring an entity to develop its own assumptions. Our Level 3 investments include investments in the equity securities of publicly-held biotechnology companies for which we calculated a lack of marketability discount because there are restrictions on when we can trade the securities. The majority of our securities have been classified as Level 2. We obtain the fair value of our Level 2 investments from our custodian banks or from a professional pricing service. We validate the fair value of our Level 2 investments by understanding the pricing model used by the custodian bank or professional pricing service provider and comparing that fair value to the fair value based on observable market prices. During the three months ended March 31, 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 March 31, 2013 and December 31, 2012 as follows (in thousands):

	At March 31, 2013	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 96,072	$ 91,072	$ 5,000	$ —
Corporate debt securities (2)	205,098	—	205,098	—
Debt securities issued by U.S. government agencies (2)	24,939	—	24,939	—
Debt securities issued by the U.S. Treasury (2)	13,424	13,424	—	—
Debt securities issued by states of the United States and political subdivisions of the states (2)	20,800	—	20,800	—
Investment in Regulus Therapeutics Inc.	44,863	—	—	44,863
Equity securities (3)	2,619	2,619	—	—
Total	$ 407,815	$ 107,115	$ 255,837	$ 44,863

	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 consolidated balance sheet.

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

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

We classified the fair value measurements of our investments in the equity securities of Regulus and Sarepta Therapeutics, Inc., or Sarepta, as Level 3. We calculated a lack of marketability discount on the fair value of these investments because there were restrictions on when we could trade 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

Table of Contents

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. As of March 31, 2013, our Level 3 investments consisted of our investment in Regulus, with a gross fair value of $54.6 million and a lack of marketability discount of $9.7 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, and a lack of marketability discount of $10.8 million and $296,000, 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 three months ended March 31, 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)	11,716
Cost basis of shares sold	(40)
Balance at March 31, 2013	$ 44,863

Other Fair Value Disclosures

Our 2¾ percent convertible notes had a fair value of $258.0 million at March 31, 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. 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 March 31,	
	2013	2012
Partner A	58%	71%
Partner B	23%	9%

Contract receivables from four significant partners comprised approximately 88 percent of our contract receivables at March 31, 2013. Contract receivables from four significant partners comprised approximately 83 percent of our contract receivables at December 31, 2012.

6. Income Taxes

Intraperiod tax allocation rules require us to allocate our provision for income taxes between continuing operations and other categories of earnings, such as other comprehensive income. In periods in which we have a year-to-date pre-tax loss from continuing operations and pre-tax income in other categories of earnings, such as other comprehensive income, we must allocate the tax provision to the other categories of earnings. We then record a related tax benefit in continuing operations. During the first quarter 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 $64,000 tax benefit on our condensed consolidated statements of operations and a $3.6 million tax expense in other comprehensive income for the three months ended March 31, 2013.

7. Collaborative Arrangements and Licensing Agreements

Traditional Pharmaceutical Alliances and Licensing

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 spinal muscular atrophy, or SMA. Under the terms of the agreement, we received an upfront payment of $29 million and are eligible to receive up to $45 million in substantive milestone payments associated with the clinical development of ISIS-SMN$_{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 initiates the Phase 2/3 program for ISIS-SMN$_{Rx}$.

We will earn a $3.5 million milestone payment from Biogen Idec when we dose the first infant in this Phase 2 study, which we project will be May 2013. The $3.5 million milestone payment is the first of four payments under the March 2013 amendment to the payment terms for the next potential $18 million milestone payment we could earn for the progression of this Phase 2/3 study in infants. 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}$.

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 months ended March 31, 2013 and 2012, we earned revenue of $3.9 million and $1.8 million, respectively, from our relationships with Biogen Idec. Our balance sheets at March 31, 2013 and December 31, 2012 included deferred revenue of $59.2 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. Our shared funding of development expenses will end when KYNAMRO is profitable.

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

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

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

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

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

The price Genzyme paid for our common stock represented a significant premium over the then fair value of our common stock. In May 2012, we finished amortizing this $100 million premium along with the $175 million licensing fee that we received in the second quarter of 2008. During the three months ended March 31, 2013 and 2012, we earned revenue of $25.0 million and $16.4 million, respectively, from our relationship with Genzyme, which represented 58 percent and 71 percent, respectively, of our total revenue for those periods. Our balance sheets at both March 31, 2013 and December 31, 2012 included deferred revenue of $3.8 million that Genzyme paid for KYNAMRO drug substance.

GlaxoSmithKline

In March 2010, we entered into a strategic alliance with GSK, which covers 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.

Under the terms of the original agreement, which includes five programs in addition to the transthyretin, or TTR, 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 will be responsible for all further development and commercialization. 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}. We have already earned $17.5 million in milestone payments from GSK related to the development of ISIS-TTR_{Rx}, and we are eligible to earn an additional $50 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} achieve registration and meet certain sales thresholds.

Under the terms of the amended agreement, if GSK successfully develops all six programs for one or more indications and achieves pre-agreed sales targets, we could receive license fees and substantive milestone payments of more than $1.3 billion, including up to $231.5 million for the achievement of development milestones, up to $594.5 million for the achievement of regulatory milestones and up to $545 million for the achievement of commercialization milestones. We will earn the next milestone payment of $2 million upon dosing the 10^{th} patient in 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.

Table of Contents

During the three months ended March 31, 2013 and 2012, we earned revenue of $9.9 million and $2.0 million, respectively, from our relationship with GSK, which represented 23 percent and nine percent, respectively, of our total revenue for those periods. Our balance sheets at March 31, 2013 and December 31, 2012 included deferred revenue of $17.6 million and $19.9 million, respectively, related to the upfront and expansion payments.

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 upon initiation of a Phase 1 Trial for a drug targeting HTT protein.

External Project Funding

CHDI Foundation, Inc.

Since November 2007, CHDI has 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 its support of our 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 will record as research and development expense in the second quarter of 2013. We will also pay CHDI $1.5 million when we select a development candidate and if we achieve certain milestones under our collaboration with Roche we will make additional payments to CHDI. During the three months ended March 31, 2013 and 2012, we earned revenue of $293,000 and $1.2 million, respectively, from our relationship with CHDI. Our balance sheet at December 31, 2012 included deferred revenue of $229,000 related to our relationship with CHDI.

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

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

Forward-Looking Statements

In addition to historical information contained in this Report on Form 10-Q, this Report includes forward-looking statements regarding our business, the therapeutic and commercial potential of our technologies and products in development, and the financial position of Isis Pharmaceuticals, Inc. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs, 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 30 of this Report.

Table of Contents

Overview

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

Our partnering strategy provides us the flexibility to license each of our drugs at the optimal time to maximize the near- and long-term value for each drug. In this way, we can expand our and our partners' pipelines with antisense drugs that we design to address significant medical needs while remaining small and focused. 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 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-term licensing opportunities. These drugs, including ISIS-APOCIII$_{Rx}$, 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.

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 $125 million in upfront payments and have the potential to earn more than $2.8 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 $5.5 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.

Table of Contents

We also work with a consortium of smaller companies that can exploit our drugs and technologies. We call these smaller companies our satellite companies. In this way, we benefit from the disease-specific expertise of our satellite company partners, who are advancing drugs in our pipeline in areas that

are outside of our core focus. In addition, we can maintain our broad RNA technology leadership through collaborations with companies such as Alnylam Pharmaceuticals, Inc., or Alnylam, and Regulus Therapeutics Inc., or Regulus, a company we co-founded with Alnylam focused on microRNA therapeutics. In October 2012, Regulus completed an initial public offering. As of March 31, 2013, the carrying value of our investment in Regulus was $44.9 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

Corporate and Drug Development Highlights

- We and Genzyme were successful in bringing KYNAMRO to the market in the United States for patients with HoFH. These patients are at high cardiovascular risk and may not be able to reduce their LDL-C sufficiently with currently available lipid-lowering therapies.
  - Genzyme launched KYNAMRO in the United States for the treatment of patients with HoFH.
    - We received a $25 million milestone payment from Genzyme related to the marketing approval of KYNAMRO by the FDA.
  - Genzyme continues to enroll the FOCUS FH study, which is designed to provide 60-week safety and efficacy data in FH patients to support an additional regulatory filing. Genzyme reached an agreement with the FDA on the design of the FOCUS FH study via a Special Protocol Assessment, or SPA.
- We and our investigators reported positive data from a number of drugs in our pipeline.
  - Dr. Claudia Chiriboga reported Phase 1 data on ISIS-SMN_{Rx} at the American Academy of Neurology. In this open-label study conducted in a small population, ISIS-SMN_{Rx} was well tolerated in children with SMA and functional activity improvements in muscle function were observed in a number of these children.
  - We reported positive Phase 1 data on ISIS-CRP_{Rx} demonstrating that, in healthy volunteers, ISIS-CRP_{Rx} can selectively blunt severe increases in CRP following an endotoxin challenge, which produces immune responses similar to those seen with bacterial infections.
  - We published data in the journal Circulation Research demonstrating that antisense inhibition of ApoC-III produced significant reductions of ApoC-III and triglycerides in multiple species including man. We presented these data in an oral presentation at the 2013 Duell Meeting in March 2013.
- We continued to advance our pipeline by initiating clinical studies in numerous disease areas.
  - We initiated a Phase 2 study of ISIS-SMN_{Rx} in infants with SMA and will earn a $3.5 million milestone payment from Biogen Idec when the first patient is dosed in this study.
  - We initiated a Phase 2/3 study of ISIS-TTR_{Rx} in patients with familial polyneuropathy and received a $7.5 million milestone payment from GSK related to the initiation of this study.
  - AstraZeneca initiated a Phase 1b/2a study of ISIS-$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 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 we 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.

Table of Contents

Critical Accounting Policies

We prepare our condensed consolidated financial statements in conformity with accounting principles generally accepted in the United States of America. As such, we make certain estimates, judgments and assumptions that we believe are reasonable, based upon the information available to us. These judgments involve making estimates about the effect of matters that are inherently uncertain and may significantly impact our quarterly or annual results of operations and financial condition. Each quarter, our senior management discusses the development, selection and disclosure of such estimates with our audit committee of our board of directors. In the following paragraphs, we describe the specific risks associated with these critical accounting policies. For all of these policies, we caution that future events rarely develop exactly as one may expect, and that best estimates may require adjustment.

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

- Assessing the propriety of revenue recognition and associated deferred revenue;
- Determining the proper valuation of investments in marketable securities and other equity investments;
- Assessing the recoverability of long-lived assets, including property and equipment, intellectual property and licensed technology;
- Determining the proper valuation of inventory;
- Determining the appropriate cost estimates for unbilled preclinical studies and clinical development activities;
- Estimating our net deferred income tax asset valuation allowance;

- Determining the fair value of convertible debt without the conversion feature;
- Determining when we are the primary beneficiary for entities that we identify as variable interest entities; and
- Determining the fair value of stock-based compensation, including the expected life of the option, the expected stock price volatility over the term of the expected life and estimated forfeitures.

There have been no material changes to our critical accounting policies and estimates from the information provided in Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations", included in our Annual Report on Form 10-K for the year ended December 31, 2012.

Results of Operations

Revenue

Total revenue for the three months ended March 31, 2013 was $43.4 million compared to $23.2 million for the same period 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, our revenue in the first quarter of 2013 was significantly higher than in the first quarter of 2012 primarily as a result of the $25 million milestone payment from Genzyme for FDA approval of the KYNAMRO NDA and the $7.5 million milestone payment from GSK for the initiation of the Phase 2/3 study of ISIS-TTR$_{Rx}$. Also in the first quarter of 2013 we began amortizing revenue from our new alliance with AstraZeneca and our third collaboration with Biogen Idec. Our increase in revenue was offset, in part, by the completion of the amortization of the upfront payments associated with our Genzyme collaboration.

In April 2013, we formed a new alliance with Roche to develop treatments for Huntington's disease, or HD. As a result, we received an upfront fee of $30 million, which we will begin amortizing into revenue over our period of performance starting in the second quarter of 2013.

Table of Contents

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for the three months ended March 31, 2013 was $41.9 million compared to $21.8 million for the same period in 2012. The increase in the first quarter of 2013 was primarily a result of the $25 million milestone payment from Genzyme, the $7.5 million milestone payment from GSK, and new revenue from our recent alliance with AstraZeneca and our third collaboration with Biogen Idec partially offset by the completion of the amortization period for the upfront payments associated with our Genzyme collaboration.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties was unchanged at $1.4 million for the three months ended March 31, 2013 and March 31, 2012.

Operating Expenses

Operating expenses for the three months ended March 31, 2013 and 2012 were $41.7 million.

In order to analyze and compare our results of operations to other similar companies, we believe it is important to exclude non-cash compensation expense related to equity awards from our operating expenses. We believe non-cash compensation expense is not indicative of our operating results or cash flows from our operations. Further, we internally evaluate the performance of our operations excluding it.

Research 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 March 31,	
	2013	2012
Research and development expenses	$ 35,766	$ 36,779
Non-cash compensation expense related to equity awards	2,546	1,935
Total research and development	$ 38,312	$ 38,714

For the three months ended March 31, 2013, our total research and development expenses were $35.8 million, slightly lower compared to $36.8 million for the same period in 2012 primarily due to lower development costs because of the timing of when studies were initiated and lower expenses related to KYNAMRO offset, in part, by higher litigation costs for our patent infringement lawsuit against Santaris Pharma A/S. 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.

Table of Contents

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

	Three Months Ended March 31,	
	2013	2012
Antisense drug discovery expenses	$ 9,397	$ 8,364
Non-cash compensation expense related to equity awards	769	565
Total antisense drug discovery	$ 10,166	$ 8,929

Antisense drug discovery costs for the three months ended March 31, 2013 were $9.4 million, compared to $8.4 million for the same period in 2012. The higher expenses in the first quarter of 2013 compared to the same period in 2012 were primarily due to higher expenses for personnel and laboratory supplies required to support our research efforts. All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Development

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

	Three Months Ended March 31,	
	2013	2012
KYNAMRO	$ 1,943	$ 3,035
ISIS-TTR$_{Rx}$	767	1,269
Other antisense development products	9,878	10,928
Development overhead costs	1,816	1,901
Non-cash compensation expense related to equity awards	856	657
Total antisense drug development	$ 15,260	$ 17,790

Antisense drug development expenses were $14.4 million for the three months ended March 31, 2013, compared to $17.1 million for the same period in 2012. Expenses in the first quarter of 2013 were lower compared to the same period in 2012 primarily due to the timing of when studies were initiated and lower expenses related to KYNAMRO. For example, we initiated a Phase 2/3 clinical study for ISIS-TTR$_{Rx}$ in February 2013 and we expect expenses for this study to increase 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 16 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.

Table of Contents

Manufacturing and Operations

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

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

	Three Months Ended March 31,	
	2013	2012
Manufacturing and operations	$ 4,220	$ 4,571
Non-cash compensation expense related to equity awards	354	262
Total manufacturing and operations	$ 4,574	$ 4,833

Manufacturing and operations expenses were $4.2 million for the three months ended March 31, 2013 and decreased slightly compared to $4.6 million for the same period in 2012. 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 costs (in thousands):

	Three Months Ended March 31,	
	2013	2012
Personnel costs	$ 2,340	$ 2,267
Occupancy	1,646	1,729
Depreciation and amortization	1,080	1,139
Insurance	287	309
Other	2,392	1,267
Non-cash compensation expense related to equity awards	567	451
Total R&D support expenses	$ 8,312	$ 7,162

R&D support costs for the three months ended March 31, 2013 were $7.8 million, compared to $6.7 million for the same period in 2012. Expenses increased in the first quarter 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 March 31,	
	2013	2012
General and administrative expenses	$ 3,100	$ 2,644
Non-cash compensation expense related to equity awards	323	332
Total general and administrative expenses	$ 3,423	$ 2,976

Table of Contents

General and administrative expenses were $3.1 million for the three months ended March 31, 2013, and increased slightly compared to $2.6 million for the same period 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 months ended March 31, 2013, compared to equity in net loss of Regulus of $976,000 for the same period 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.

Investment Income

Investment income for the three months ended March 31, 2012 was $376,000, compared to $600,000 for the same period in 2012. The decrease in investment income was primarily due to a lower average return on our investments resulting from current market conditions.

Interest Expense

Interest expense for the three months ended March 31, 2013 was $4.8 million, compared to $5.2 million for the same period 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 months ended March 31, 2013 was $1.1 million, compared to $17,000 for the same period in 2012. The gain on investments in the first quarter of 2013 was due to the $1.1 million we realized when we sold the stock we held in Sarepta Therapeutics. This gain demonstrates the value that we are realizing from our satellite company strategy.

Income Tax Benefit (Expense)

We recorded a tax benefit of $64,000 for the three months ended March 31, 2013, compared to tax expense of $2,000 for the same period in 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 three months of 2013.

Net Loss and Net Loss per Share

Net loss for the three months ended March 31, 2013 was $1.7 million, compared to $24.0 million for the same period in 2012. Basic and diluted net loss per share for the three months ended March 31, 2013 was $0.02 per share, compared to $0.24 per share for the same period in 2012. Our net loss was significantly lower than the same period in 2012 primarily due to the improvement in our operating results.

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 March 31, 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 March 31, 2013, we have raised net proceeds of approximately $845.1 million from the sale of our equity securities and we have borrowed approximately $784.4 million under long-term debt arrangements to finance a portion of our operations.

As of March 31, 2013, we had cash, cash equivalents and short-term investments of $371.9 million and stockholders' equity of $201.1 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. At March 31, 2013, we had consolidated working capital of $361.5 million, compared to $349.1 million at December 31, 2012. We maintained our strong cash position primarily due to the $32.5 million in milestone payments we received in the first quarter of 2013. Our cash at March 31, 2013 does not include the $30 million upfront payment we received from Roche for our HTT collaboration. Our working capital increased in 2013 primarily due to an increase in current assets resulting from an increase in our investment in Regulus. At March 31, 2013, the carrying value of our investment in Regulus was $44.9 million compared to $33.6 million at December 31, 2012.

Table of Contents

As of March 31, 2013, our debt and other obligations totaled $283.0 million, compared to $284.1 million at December 31, 2012. The decrease was primarily due to rent and principal payments we made in the first three months of 2013 on our lease obligations and notes payable.

The following table summarizes our contractual obligations as of March 31, 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)	$ 240.0	$ 5.5	$ 11.1	$ 11.1	$ 212.3
Facility Rent Payments	$ 142.3	$ 5.9	$ 12.5	$ 13.2	$ 110.7
Equipment Financing Arrangements (principal and interest payable)	$ 9.1	$ 4.6	$ 4.5	$ —	$ —
Other Obligations (principal and interest payable)	$ 1.4	$ 0.1	$ 0.1	$ 0.1	$ 1.1
Capital Lease	$ 0.5	$ 0.2	$ 0.3	$ —	$ —
Operating Leases	$ 27.2	$ 1.5	$ 2.7	$ 2.8	$ 20.2
Total	$ 420.5	$ 17.8	$ 31.2	$ 27.2	$ 344.3

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

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

In October 2008, we entered into a loan agreement related to an equipment financing 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. As of March 31, 2013, our outstanding borrowings under this loan agreement were at a weighted average interest rate of 4.57 percent and we can borrow up to an additional $6.0 million in principal to finance the purchase of equipment until April 2014. The carrying balance under this loan agreement at March 31, 2013

and December 31, 2012 was $8.7 million and $10.0 million, respectively. We will continue to use equipment lease financing as long as the terms remain commercially attractive.

Table of Contents

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 March 31, 2013 for the purchase of services, capital equipment and materials as part of our normal course of business.

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

RISK FACTORS

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

Risks Associated with our Drug Discovery and Development Business

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

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

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

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

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

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

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

Table of Contents

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

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

- priced lower than our drugs;

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

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

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

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

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

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

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

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

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

In addition, when approved, the FDA or a foreign regulatory authority may condition approval on the performance of post-approval clinical studies or patient monitoring, which could be time consuming and expensive. If the results of such post-marketing studies are not satisfactory, the FDA or a foreign regulatory authority may withdraw marketing authorization or may condition continued marketing on commitments from us or our partners that may be expensive and/or time consuming to fulfill.

Table of Contents

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 Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency maintained a negative opinion for Genzyme's marketing authorization application for KYNAMRO as a treatment for patients with HoFH.

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

Table of Contents

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

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

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

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

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

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

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

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

To successfully commercialize any of our drugs, we or our partner would need to establish large-scale commercial manufacturing capabilities either on our own or through a third party manufacturer. In addition, as our drug development pipeline increases and matures, we will have a greater need for clinical trial and commercial manufacturing capacity. We have limited experience manufacturing pharmaceutical products of the chemical class represented by our drugs, called oligonucleotides, on a commercial scale for the systemic administration of a drug. There are a small number of suppliers for certain

capital equipment and raw materials that we use to manufacture our drugs, and some of these suppliers will need to increase their scale of production to meet our projected needs for commercial manufacturing. Further, we must continue to improve our manufacturing processes to allow us to reduce our drug costs. We may not be able to manufacture our drugs at a cost or in quantities necessary to make commercially successful products.

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

Table of Contents

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

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

Risks Associated with our Businesses as a Whole

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

Because drug discovery and development requires substantial lead-time and money prior to commercialization, our expenses have generally exceeded our revenue since we were founded in January 1989. As of March 31, 2013, we had an accumulated deficit of approximately $908.6 million and stockholders' equity of approximately $201.1 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 and Teva Pharmaceutical Industries Ltd. 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.

Table of Contents

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 Committee for Medicinal Products for Human Use (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.

Table of Contents

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 March 31, 2013, we had cash, cash equivalents and short-term investments equal to $371.9 million. If we do not meet our goals to commercialize KYNAMRO or our other drugs, or to license our drugs and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

- 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 March 31, 2013, the market price of our common stock ranged from $7.02 to $19.53 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.

Table of Contents

We are exposed to potential product liability claims, and insurance against these claims may not be available to us at a reasonable rate in the future or at all.

Our business exposes us to potential product liability risks that are inherent in the testing, manufacturing, marketing and sale of therapeutic products, including potential product liability claims related to KYNAMRO. We have clinical study insurance coverage and commercial product liability insurance coverage. However, this insurance coverage may not be adequate to cover claims against us, or be available to us at an acceptable cost, if at all. Regardless of their merit or eventual outcome, products liability claims may result in decreased demand for our drug products, injury to our reputation, withdrawal of clinical study volunteers and loss of revenues. Thus, whether or not we are insured, a product liability claim or product recall may result in losses that could be material.

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

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

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

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

We depend on Regulus for development of our microRNA technology.

Regulus is a company that we and Alnylam established to focus on discovering, developing, and commercializing microRNA therapeutics. We exclusively licensed to Regulus our intellectual property rights covering microRNA technology. Regulus operates as an independent company and Regulus and its employees are 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.

Table of Contents

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

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

Our certificate of incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. In addition, only our board of directors, chairman of the board or chief executive officer can call special meetings of our stockholders. We have in the past, and may in the future, implement a stockholders' rights plan, also called a poison pill, which could make it uneconomical for a third party to acquire our company on a hostile basis. In addition, our board of directors has the authority to fix the rights and preferences of, and issue shares of preferred stock, which may have the effect of delaying or preventing a change in control of our company without action by our stockholders.

The provisions of our convertible senior notes could make it more difficult or more expensive for a third party to acquire us. Upon the occurrence of certain transactions constituting a fundamental change, holders of the notes will have the right, at their option, to require us to repurchase all of their notes or a portion of their notes, which may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over the then current market prices.

In addition, our collaboration agreement with Genzyme regarding KYNAMRO provides that if we are acquired, Genzyme may elect to purchase all of our rights to receive payments under the KYNAMRO collaboration agreement for a purchase price to be mutually agreed to by us and Genzyme, or, if we cannot agree, a fair market value price determined by an independent investment banking firm. This provision may make it more difficult or complicated for us to enter into an acquisition agreement with a potential acquirer.

These provisions, as well as Delaware law, including Section 203 of the Delaware General Corporation Law, and other of our agreements, may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over then current market prices, and may limit the ability of our stockholders to approve transactions that they think may be in their best interests.

Future sales of our common stock in the public market could adversely affect the trading price of our securities.

Future sales of substantial amounts of our common stock in the public market, or the perception that such sales could occur, could adversely affect trading prices of our securities. For example, we may issue approximately 12.1 million shares of our common stock upon conversion of our convertible senior notes. The addition of any of these shares into the public market may have an adverse effect on the price of our securities.

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

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

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

Table of Contents

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

The global credit markets, the financial services industry, the U.S. capital markets, and the U.S. economy as a whole have been experiencing a period of substantial turmoil and uncertainty characterized by unprecedented intervention by the U.S. federal government and the failure, bankruptcy, or sale of various financial and other institutions. The impact of these events on our business and the severity of the economic crisis are uncertain. It is possible that the crisis in the global credit markets, the U.S. capital markets, the financial services industry and the U.S. economy may adversely affect our business, vendors and prospects as well as our liquidity and financial condition. More specifically, our insurance carriers and insurance policies covering all aspects of

our business may become financially unstable or may not be sufficient to cover any or all of our losses and may not continue to be available to us on acceptable terms, or at all.

ITEM 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

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

ITEM 4. CONTROLS AND PROCEDURES

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. Based on this evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of March 31, 2013. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to March 31, 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.

Table of Contents

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

Table of Contents

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.1	Letter agreement dated March 3, 2013 between the Registrant and Biogen Idec International Holding Ltd.
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 March 31, 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 loss, (iv) condensed consolidated statements of cash flows and (v) notes to condensed consolidated financial statements (detail tagged).

Isis Pharmaceuticals, Inc.

(Registrant)

Table of Contents

SIGNATURES

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

Signatures	Title	Date
/s/ Stanley T. Crooke Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	May 7, 2013
/s/ Elizabeth L. Hougen Elizabeth L. Hougen	Senior Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	May 7, 2013

Exhibit 10.1

March 13, 2013

Richard Brudnick
Vice President, Co-Head Business Development/M&A
Biogen Idec MA Inc.
14 Cambridge Center
Cambridge, MA 02142

M Tonesan Naa-Lamle Amissah
Biogen Idec International Holding Ltd.
Appleby (Bermuda) Ltd.
Canon's Court, 22 Victoria Street
Hamilton HM 12
Bermuda

Dear Richard,

Isis and Biogen Idec are parties to the Development, Option and License Agreement dated January 3, 2012 (the ***"SMA Agreement"***) and wish to specify the payment schedule for the $18 million Initiation of the CS3 Study Pre-Licensing Milestone Event under the SMA Agreement.

As such, Isis and Biogen Idec agree the $18 million payment for the Initiation of the CS3 Study Pre-Licensing Milestone Event under the SMA Agreement is due as follows and payable within 45 days of receipt of invoice following the applicable event:

a. $3.5 million will be due upon the dosing of the first patient in the first cohort of the ISIS 396443-CS3A Study to Assess the Safety, Tolerability, and Pharmacokinetics of Multiple Doses of ISIS 396443 Delivered Intrathecally to Patients with Infantile-Onset Spinal Muscular Atrophy) (the ***"CS3A Study"***);

b. $2.0 million will be due upon the dosing of the first patient in the second cohort of the CS3A Study;

c. $1.5 million will be due upon the dosing of the eighth patient in the second cohort of the CS3A Study; and

d. $11 million will be due upon the dosing of the first patient in the Infantile-Onset Spinal Muscular Atrophy Registration Study (CS3B).

Except as set forth above, any other provisions of the SMA Agreement will remain in full force and effect. Capitalized terms used but not defined herein will have the meaning ascribed to such terms in the SMA Agreement.

This letter agreement may be signed in counterparts, each of which will be deemed an original. Facsimile signatures and signatures transmitted via electronic mail in PDF format will be treated as original signatures.

IN WITNESS WHEREOF, Isis and Biogen Idec have caused this letter agreement to be executed by their representatives as of the date hereof.

BIOGEN IDEC INTERNATIONAL HOLDING LTD

/s/ M. Tonesan N. Amissah
M. Tonesan N. Amissah

Director, Biogen Idec International Holding Ltd.

ISIS PHARMACEUTICALS, INC.

/s/ B. Lynne Parshall
/s/ B. Lynne Parshall
Chief Operating Officer

EXHIBIT 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: May 7, 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: May 7, 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 March 31, 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: May 7, 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.