August 12, 2011

United States Securities and Exchange Commission
Division of Corporate Finance
Attn: Jim B. Rosenberg, Senior Assistant Chief Accountant
100 F Street, NE
Washington, D.C. 20549

Re: Isis Pharmaceuticals, Inc.
Form 10-K for the Year Ended December 31, 2010
Form 10-Q for the Quarterly Period Ended March 31, 2011
Schedule 14A
File No. 000-19125

Dear Mr. Rosenburg:

On behalf of Isis Pharmaceuticals, Inc. (the "Company," "Isis" or "we"), enclosed for electronic filing via EDGAR pursuant to the Securities Act of 1933, please find responses to your comments in reference to the Company's Form 10-K for the fiscal year ended December 31, 2010; Form 10-Q for the quarterly period ended March 31, 2011; and Schedule 14A for the 2011 Annual Meeting of Stockholders, File No. 000-19125.

As requested by the Staff in your letter, please find below our response to your comments and our proposed disclosure to be included in future periodic reports.

Form 10-K for the Year Ended December 31, 2010
Business
Collaborative Arrangements and Licensing Agreements, page 17

1. *Please provide proposed disclosure to be included in future periodic reports to include the following additional information of your November 2001 agreement with OncoGenex and your January 2008 agreement with Genzyme:*

    - *All material rights conferred and obligations assumed for and by both parties to the agreements,*
    - *The nature of material patents and their jurisdiction and expiration dates, know-how or other intellectual property licensed or transferred in the agreements,*
    - *Geographic, product, indication and other forms of exclusivity provided for in the agreements,*
    - *The provisions regarding the termination of the agreements, and*
    - *The duration of the agreements including the effect of patent expirations or marketing exclusivity, as applicable.*

Explain whether the company was a party to or how the company otherwise consented to the December 2009 agreement transferring the rights to distribute OGX-011 to Teva. Indicate whether Teva was granted exclusive or more limited rights to the product and provide the same information regarding this agreement as requested above regarding the Genzyme and OncoGenex agreements.

In response to your request to explain whether we consented to, or were a party to, the December 2009 agreement pursuant to which OncoGenex transferred to Teva rights to distribute OGX-011, we note that under our agreement with OncoGenex, OncoGenex had the right to transfer to Teva *via* sublicense, OncoGenex's rights to develop and commercialize OGX-011 that OncoGenex received from Isis. Our agreement with OncoGenex allowed OncoGenex to grant such rights without Isis' consent, in exchange for OncoGenex sharing with Isis a percentage of the payments OncoGenex receives from Teva resulting from such a transfer. As such, we did not grant OncoGenex a formal consent, or enter into an agreement with Teva in connection with the sublicense from OncoGenex to Teva to distribute OGX-011 to Teva. OncoGenex has not provided us with an unredacted copy of OncoGenex's agreement with Teva, so we can only base our understanding about OncoGenex's agreement with Teva on the information OncoGenex has made publicly available. According to OncoGenex's Annual Report on Form 10-K for the year ended December 31, 2010, Teva received the exclusive worldwide right and license to develop and commercialize any products containing OGX-011 and related compounds, with OncoGenex having an option to co-promote OGX-011 in the United States and Canada. Since Isis does not have a direct agreement with Teva, and we are generally reluctant to rely on another party's statements when writing our disclosures that are subject to liability under the securities laws, we respectfully submit that it would be inappropriate and difficult for us, and potentially confusing to our stockholders, to provide the same level of detail regarding OncoGenex's agreement with Teva as the Staff has requested we provide regarding our agreements with OncoGenex and Genzyme.

In response to your request to provide proposed disclosure to include additional information regarding our November 2001 agreement with OncoGenex and our January 2008 agreement with Genzyme, we propose to include the disclosure set forth on:

- Attachment A to this letter with respect to OncoGenex (marked to indicate changes from language in previous Form 10-K); and
- Attachment B to this letter with respect to Genzyme (marked to indicate changes from language in previous Form 10-K).

Regarding OncoGenex, we direct the Staff's attention to the following pages and line numbers of Attachment A:

- *Regarding all material rights conferred and obligations assumed for and by both parties to the agreements,*
    - Please see Page A-1 of Appendix A; lines 11-17, 26-32 and 38-42; and Page A-2 of Appendix A; lines 5-14.

- *Regarding the nature of material patents and their jurisdiction and expiration dates, know-how or other intellectual property licensed or transferred in the agreements,*
  - Please see Page A-1 of Appendix A; lines 18-26.
- *Regarding geographic, product, indication and other forms of exclusivity provided for in the agreements,*
  - Please see Page A-1 of Appendix A; lines 18-29.
- *Regarding the provisions regarding the termination of the agreements, and*
  - Please see Page A-1 of Appendix A; lines 26-32 and 40-42; and Page A-2 of Appendix A; lines 1-2.
- *Regarding the duration of the agreements including the effect of patent expirations or marketing exclusivity, as applicable.*
  - Please see Page A-1 of Appendix A; lines 26-32 and 40-42; and Page A-2 of Appendix A; lines 1-2.

Regarding Genzyme, we direct the Staff's attention to the following pages and line numbers of Attachment B:

- *Regarding all material rights conferred and obligations assumed for and by both parties to the agreements,*
  - Please see Page B-1 of Appendix B; lines 6-15 and 21-30; and Page B-2 of Appendix B; lines 4-25.
- *Regarding the nature of material patents and their jurisdiction and expiration dates, know-how or other intellectual property licensed or transferred in the agreements,*
  - Please see Page B-1 of Appendix B; lines 7-15.
- *Regarding geographic, product, indication and other forms of exclusivity provided for in the agreements,*
  - Please see Page B-1 of Appendix B; lines 7-15.
- *Regarding the provisions regarding the termination of the agreements, and*
  - Please see Page B-1 of Appendix B; lines 32-40; and Page B-2 of Appendix B; lines 1-15.
- *Regarding the duration of the agreements including the effect of patent expirations or marketing exclusivity, as applicable.*
  - Please see Page B-1 of Appendix B; lines 32-40; and Page B-2 of Appendix B; lines 1-10. We note that because our agreement with Genzyme is structured as a profit sharing arrangement, patent and market exclusivity do not impact Genzyme's obligations to share profits with us.

Form 10-Q for the Quarterly Period Ended March 31, 2011
Notes to Condensed Consolidated Financial Statements
2. Significant Accounting Policies
Revenue Recognition
Research and development revenue under collaborative agreements, page 6

2. *Please provide proposed disclosure to be included in future periodic reports that addresses the following for each arrangement under which you may earn milestone revenue in accordance with ASC 605-28-50-2:*

   - *A description of each milestone and related contingent consideration; and,*
   - *A determination of whether each milestone is considered substantive.*

In response to your inquiry about our disclosure related to the milestone payments we may earn from our partners, we believe it will be helpful for you to understand the critical role partnerships play in our business strategy. Our business strategy is to discover unique antisense drugs and develop these drugs to key clinical value inflection points. We discover and conduct early development of new drugs, outlicense our drugs to partners and build a broad base of potential license fees, milestone payments and royalty income. We do not intend to become a fully-integrated pharmaceutical company that manufactures, markets and sells its drugs. Rather, we maximize the value of our drugs by putting them in the hands of quality partners with late-stage development, regulatory and commercialization expertise. As a result of our unique business strategy, we routinely enter into partnership agreements which contain milestones generally connected to key development, regulatory and commercialization events. The related milestone payments are only one element of the overall economics of our transactions, which are highly negotiated. Disclosure of specific financial terms such as milestone payments would provide potential partners with competitive information about the specific financial terms of our transactions, and the value we place on different components of our technology, thereby making it very difficult, if not impossible, for us to negotiate the best possible financial terms for a transaction. In addition, in some cases disclosing the specific milestone events and the associated value we and our partner place on achieving the event would give our competitors who are developing similar drugs or technology valuable insight into our development plans and strategy. These competitors can use this information to alter their own development strategies to better compete with us and our partners. Further, we do not have access to similar information from biotechnology and pharmaceutical industry companies and thus would be at a significant competitive disadvantage were we to disclose specific milestone information. In summary, the nature of the information requested is highly confidential[(1)] and disclosure of the specific negotiated financial terms in our agreements, including potential milestone payments, would cause us substantial competitive harm to the detriment of our stockholders.

[(1)] In fact, we believe detailed milestone information is confidential commercial and financial information that is subject to protection under 17 C.F.R. §§ 200.80(b)4, and 240.24b-2.

To balance your request and the highly confidential nature of the requested information, we believe that breaking down our milestones into significant categories would provide the users of our financial statements with meaningful details about the milestone payments we potentially could earn while not adversely impacting our business. In conjunction with our proposed breakdown of our milestones into significant categories, we believe it is important to provide additional disclosure in our financial statements about how the milestones tie into the life-cycle of our drugs.

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 which 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 preclinical studies, which are animal studies intended to support an Investigational New Drug ("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 proper dose and potential 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 ("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 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. The process of successfully discovering a new development candidate, having it approved and ultimately sold for a profit is highly uncertain. Therefore, as a drug progresses through the stages of its life-cycle, the value of the drug generally increases.

In our current Form 10-K filing, we have included a significant amount of disclosure about the key terms of each of our material partnerships including the aggregate amount of potential milestone payments we can earn under each arrangement. To enhance our existing disclosure, we feel it is meaningful to add an additional breakdown of our potential milestone payments into the following categories, which tie into the life-cycle of our drugs as described above:

- Development milestones;
- Regulatory milestones; and
- Commercialization milestones.

By breaking down our milestones into significant categories, we provide the users of our financial statements with valuable information about the nature and dollar amount of our potential milestone payments. Additionally, since these categories correspond to the life-cycle of our drugs, the users of our financial statements can estimate the approximate timing of our potential milestone payments using the extensive information we provide in the business section of our filings. Since each of our partnership agreements are unique and can vary depending on the particular facts and circumstances, if the above mentioned categories do not adequately characterize a particular agreement, we will add and/or delete categories as appropriate.

In response to your request to provide proposed disclosure to address the information requested in the first bullet point of ASC 605-28-50-2, we propose to include in our future filings for each of our significant agreements with potential milestone payments the following general form of disclosure in the financial statement footnotes:

Under our collaboration agreement with ABC Pharmaceuticals, Inc. we may receive up to $XX million in substantive milestone payments upon the achievement of pre-specified events, including up to $XX million for the achievement of development milestones, up to $XX million for the achievement of regulatory milestones and up to $XX million for the achievement of commercialization milestones.

In response to your request to provide proposed disclosure to address the information requested in the second bullet point of ASC 605-28-50-2, we propose adding additional disclosure to our significant accounting policies describing the life-cycle of our drugs, the typical events that comprise the significant categories that we use to break down our milestones and the factors we evaluate to determine whether our milestones are substantive. We have reflected our proposed changes in a copy of our revenue recognition policy taken from our second quarter Form 10-Q filed on August 8, 2011 and included here as Attachment C. The proposed changes are marked to show changes from our current disclosure.

Schedule 14A filed April 28, 2011
Cash Bonus — At Risk, page 39
Cash Bonus, page 39

3. *Please provide proposed disclosure to be included in future periodic reports to include the following additional information regarding the NEOs other than the CEO;*

   - *The specific MBO percentages employed for each NEO,*
   - *The specific individual success factors employed for each NEO, and*
   - *The evaluation of each NEO's individual performance for the purpose of setting the applicable individual success factors including the specific facts and results considered by the CEO and the Committee.*

In response to your request to include in future periodic reports additional information about our NEOs, other than the CEO, we propose to include the requested information in our next Annual Report on Form 10-K (which may be included by incorporation by reference to our DEF 14A) and our DEF 14A using the following format (in the same location as the cash bonus information Isis provided regarding its CEO in the last DEF 14A):

Once the Compensation Committee has determined the elements of the formula above, the formula is applied to each executive officer. Applying this formula, the Compensation Committee approved the following cash bonus for our named executive officers, using the criteria set forth in the table below to set each individual's Individual Success Factor:

Name	Base Salary	Target MBO %	Company Success Factor	Individual Success Factor	Resulting Bonus	Key Results Considered when Setting Individual Success Factor
Stanley T. Crooke						
B. Lynne Parshall						
C. Frank Bennett						
Richard S. Geary						

* * * *

In connection with this response, we acknowledge the following:

- The company is responsible for the adequacy and accuracy of the disclosure in the filings;
- Staff comments or changes to disclosure in response to staff comments do not foreclose the Commission from taking any action with respect to the filings; and
- The company may not assert staff comments as a defense in any proceeding initiated by the Commission or any person under the federal securities laws of the United States.

Should you have any questions regarding our responses or require any additional information, please contact Elizabeth Hougen, Vice President Finance and Chief Accounting Officer, at (760) 603-2492 or me at (760) 603-2460.

Sincerely,

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

Attachments:
Attachment A
Attachment B
Attachment C

Attachment A
Proposed Disclosure Regarding OncoGenex
(marked to show changes against language from previous Form 10-K)

OncoGenex Technologies Inc., a subsidiary of OncoGenex Pharmaceuticals Inc.

In November 2001, we established a drug development collaboration with OncoGenex, a biotechnology company committed to the development of cancer therapeutics for patients with drug resistant and metastatic cancers, to co-develop and commercialize OGX-011, an anti-cancer antisense drug that targets clusterin. In July 2008, we and OncoGenex amended the co-development agreement pursuant to which OncoGenex became solely responsible for the costs, development and commercialization of OGX-011. In exchange, OncoGenex agreed to pay us royalties on sales of OGX-011 and to share consideration it receives from licensing OGX-011 to a third party, except for consideration received by OncoGenex for the fair market value of equity and reimbursement of research and development expenses.

Under the amended agreement, we assigned to OncoGenex our rights in the patents claiming the composition and therapeutic methods of using OGX-011, and granted OncoGenex a worldwide, nonexclusive license to our know-how and patents covering our core antisense technology and manufacturing technology solely for use with OGX-011. The key product related patent that we assigned to OncoGenex was U.S. Patent number 6,900,187 having an expiration date of at least 2020; and the key core antisense technology patents we licensed OncoGenex are U.S. Patent number 7,919,472 having an expiration date of 2026 and its foreign equivalents pending in Australia, Canada, the European Patent Convention and Japan. In addition, we agreed that so long as OncoGenex or its commercialization partner is using commercially reasonable efforts to develop and commercialize OGX-011, we will not research, develop or commercialize an antisense compound designed to modulate clusterin. The amended agreement will continue until OncoGenex or its commercialization partner is no longer developing or commercializing OGX-011 or until we terminate the agreement for an uncured failure by OncoGenex to make a payment required under the agreement.

In December 2009, OncoGenex ~~licensed OGX-011 to Teva for the treatment of~~

~~multiple cancer indications~~granted Teva the exclusive worldwide right and license to develop and commercialize any products containing OGX-011 and related compounds, with OncoGenex having an option to co-promote OGX-011 in the United States and Canada, for which we received $10 million of the upfront payment OncoGenex received from Teva. We are also eligible to receive 30 percent of up to $370 million in milestone payments OncoGenex may receive from Teva in addition to ~~up to seven percent~~ royalties on sales of OGX-~~011.~~011 ranging between 3.88% and 7%. Under the agreement, this royalty is due on a country by country basis until the later of ten years following the first commercial sale of OGX-011 in the relevant country, and the expiration of the last patent

we assigned or licensed to OncoGenex that covers the making, using or selling of OGX-011 in such country.

To facilitate the execution and performance of OncoGenex's agreement with Teva, we and OncoGenex amended our license agreement primarily to give Teva the ability to cure any future potential breach by OncoGenex under our agreement. As part of this amendment, OncoGenex agreed that if OncoGenex is the subject of a change of control with a third party, where the surviving entity immediately following such change of control has the right to develop and sell OGX-011, then a milestone payment of $20 million will be due and payable to Isis 21 days following the first commercial sale of the product in the United States. Any non-royalty payments OncoGenex previously paid to us are creditable towards the $20 million milestone payment, so as a result of the $10 million payment we received from OncoGenex related to its license to Teva, the remaining amount owing in the event of a change of control as discussed above is a maximum of $10 million.

In August 2003, we and OncoGenex entered into a separate collaboration and license agreement for the development of a second-generation antisense anti-cancer drug, OGX-225. OncoGenex is responsible for all development costs and activities, and we have no further performance obligations. OncoGenex issued to us $750,000 of OncoGenex securities as payment for an upfront fee. In addition, OncoGenex will pay us milestone payments totaling up to $3.5 million for the achievement of clinical and regulatory milestones, and royalties on product sales. As of December 31, 2010, OncoGenex had not achieved any milestone events related to OGX-225.

In January 2005, we entered into a further agreement with OncoGenex to allow for the development of an additional second-generation antisense anti-cancer drug. Under the terms of the agreement, OncoGenex is responsible for all development costs and activities, and we have no further performance obligations. In April 2005, OncoGenex selected OGX-427 to develop under the collaboration. OncoGenex will pay us milestone payments totaling up to $4.2 million for the achievement of key clinical and regulatory milestones, and royalties on future product sales of the drug. As of December 31, 2010, OncoGenex had not achieved any milestone events related to OGX-427 but in January 2011, we earned a $750,000 milestone payment related to OncoGenex's phase 2 trial in men with metastatic prostate cancer.

Attachment B

Proposed Disclosure Regarding Genzyme

(marked to show changes against language from previous Form 10-K)

Genzyme Corporation

In January 2008, we entered into a strategic alliance with Genzyme focused on the licensing and co-development of mipomersen and a research relationship. The license and co-development agreement provides Genzyme with exclusive worldwide rights for all therapeutic purposes to our patents and know-how related to mipomersen, including the key product related patents described in the "Patent and Proprietary Rights" section under "ApoB and Mipomersen" on page [XX] of this report, and their foreign equivalents pending world-wide in various countries, including in the European Union via the European Patent Convention, Japan, Canada, Australia, New Zealand and India. In addition, we agreed that we would not develop or commercialize another oligonucleotide-based compound designed to modulate apolipoprotein B-100, throughout the world.

The transaction, which closed in June 2008, 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 at $30 per share, over $1.5 billion in potential milestone

payments and a share of worldwide profits on mipomersen and follow-on drugs ranging from 30 percent to 50 percent of all commercial sales.

Under this alliance, Genzyme is responsible for the continued development and commercialization of mipomersen. We agreed to supply the active pharmaceutical ingredient for mipomersen for the Phase 3 clinical trials and initial commercial launch. Genzyme is responsible for manufacturing the finished drug product for mipomersen, including the initial commercial launch supply, and, if approved, Genzyme will be responsible for the long term supply of mipomersen drug substance and finished drug product. In addition, we will contribute up to the first $125 million in funding for the development costs of mipomersen, which we expect to meet in 2011. Thereafter, we and Genzyme will share development costs equally. Our initial development funding commitment and the shared funding will end when the program is profitable. As part of our alliance, Genzyme has a first right of negotiation for ISIS-SOD1$_{Rx}$.

The license and co-development agreement for mipomersen will continue in perpetuity unless earlier terminated by us or Genzyme 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-county basis or in its entirety upon Genzyme's uncured failure to use commercially reasonable efforts to develop and commercialize mipomersen 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 mipomersen 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 mipomersen, then the rights to mipomersen will revert back to us and we may develop and commercialize mipomersen 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 mipomersen 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 that it will not sell the Isis stock that it purchased in February 2008 until the earlier of four years from the date of our mipomersen ~~License and Co-Development Agreement~~license and co-development agreement, the first commercial sale of mipomersen or the termination of our mipomersen ~~License~~license and ~~Co-Development~~co-development Agreement. Thereafter, Genzyme will be subject to monthly limits on the number of shares it can sell. In addition, Genzyme has agreed that until the earlier of the 10 year anniversary of the mipomersen ~~License and Co-Development Agreement~~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.

During 2010, 2009 and 2008, we recognized revenue of $66.9 million, $66.4 million and $48.2 million, respectively, primarily related to the amortization of the upfront payments we received from Genzyme, which represented 62 percent, 55 percent and 45 percent, respectively, of our total revenue for those years.

Attachment C
Proposed Disclosure in Significant Accounting Policies
(marked to show changes against language from second quarter 2011 Form 10-Q)

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

Research and development revenue under collaborative agreements

On January 1, 2011, we adopted an accounting standard, which amended the criteria to identify separate units of accounting for revenue arrangements with multiple deliverables. The new guidance replaces the concept of allocating revenue among deliverables in a multiple-element revenue arrangement according to fair value with an allocation based on selling price. The new standard is applicable on a prospective basis to agreements we entered into or materially modified after January 1, 2011. The adoption of the standard did not impact our financial position or results of operations as of and for the six month period ended June 30, 2011 as we did not enter into or materially modify any multiple-element arrangements during that period. However, the adoption of this standard may result in revenue recognition for future agreements that is different from our existing multiple-element arrangements.

For agreements that we entered into or materially modified prior to the adoption of the revised multiple element guidance, we recognize revenue from ~~arrangements that contain multiple deliverables from~~ each element of the arrangement as long as we can determine a standalone value for the delivered element and fair value for the undelivered elements, we have completed our obligation to deliver or perform on that element and we are reasonably assured of collecting the resulting receivable.

We often enter into collaborations with multiple deliverables under which we receive non-refundable upfront payments. For collaborations where we determine that there is a single unit of accounting, we recognize revenue related to upfront payments ratably over our estimated period of performance relating to the term of the contractual arrangements. Occasionally, we must estimate our period of performance when the agreements we entered 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 and the party responsible for performing them. 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. We have made estimates of our continuing obligations on several agreements. Adjustments to performance periods and related adjustments to revenue amortization periods have had a material impact on our revenue on only one occasion. When Alnylam Pharmaceuticals, Inc. terminated the companies' single-stranded RNAi, or ssRNAi, research program in November 2010, we recognized as revenue $4.9 million, which was the remaining deferred revenue from the upfront fee that we were amortizing into revenue over the research term.

Our collaborations often include contractual milestones, which typically relate to the achievement of pre-specified development, regulatory and commercialization events. ~~When we achieve these milestones, we are entitled to payment, according to the underlying agreements.~~ 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 which 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 (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 (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 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 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, generally, IND-enabling animal studies for a new development candidate 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 in the United States or Marketing Authorization Application 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. 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;

- ~~Substantive effort is involved to achieve the milestone event.~~ The achievement of the milestone involves substantive effort and can only be achieved based in whole or part on our performance or the occurrence of a specific outcome resulting from our performance;

- The amount of the milestone payment appears reasonable either in relation to the effort expended or to the enhancement of the value of the delivered items;

- There is no future performance required to earn the milestone; and

- The consideration is reasonable relative to all deliverables and payment terms in the arrangement.

If any of these conditions are not met, we will defer recognition of the milestone payment and recognize it as revenue over the estimated period of performance, if any. In May 2011, we initiated a Phase 1 clinical study on ISIS-TTR_{RX} , the first drug selected as part of our collaboration with GSK and in January 2011 OncoGenex Pharmaceuticals Inc., initiated a Phase 2 trial of OGX-427 in men with metastatic prostate cancer. We considered the initiation of Phase 1 and Phase 2 clinical trials to be substantive milestones because the level of effort and inherent risk associated with successfully moving a drug into Phase 1 and Phase 2 clinical development is high. Therefore, we recognized the entire $5 million milestone payment from GSK in the second quarter of 2011 and the entire $750,000 milestone payment from OncoGenex in the first quarter of 2011. Further information about our collaborative arrangements can be found in Note 6, Collaborative Arrangements and Licensing Agreements, below and Note 8 of our audited financial statements for the year ended December 31, 2010 included in our Annual Report on Form 10-K filed with the SEC.

As part of our Genzyme, a Sanofi company, strategic alliance, in February 2008 Genzyme made a $150 million equity investment in us by purchasing five million shares of our common stock at $30 per share. The price Genzyme paid for our common stock represented a significant premium over the fair value of our stock. We accounted for this premium as deferred revenue and are amortizing it along with the $175 million licensing fee that we received in June 2008 ratably into revenue until June 2012, which represents the end of our performance obligation based on the current research and development plan.

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.