October 7, 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 follow-up comments in reference to the Company's Form 10-Q for the quarterly period ended March 31, 2011, File No. 000-19125, including our proposed disclosure to be included in future periodic reports.

Form 10-Q for the Quarterly Period Ended March 31, 2011
Financial Statements
Collaborative Arrangements and Licensing Agreements

1. *We acknowledge your response to comment two. However, we believe that disclosure of each revenue milestone that you may potentially earn under the existing agreements is required under ASC 605-28-50-2. Accordingly, please revise your proposed disclosure to describe each milestone and related contingent consideration. In addition, if true, please also revise your proposed disclosure to clarify that you consider all potential milestones to be substantive.*

We Share a Common Goal of Enabling Investors to Make Informed Investment Decisions

We have the same objective as the Staff – to plainly tell investors all material information about our business and financial prospects to allow them to make informed investment decisions regarding our stock. We believe providing a detailed description of each and every revenue milestone and contingent consideration we may potentially earn under our extremely large volume of existing agreements is inconsistent with and counter to this objective.

As noted in our previous response, our business strategy is to discover unique antisense drugs and develop these drugs to key clinical value inflection points, and then outlicense our drugs to partners. In addition, a significant portion of our technology has utility outside our core antisense drug programs, so we outlicense this technology to other parties, as well. Through these partnering and licensing transactions, we have built a broad base of potential license fees, milestone payments, and royalty payments. We have successfully executed this strategy, resulting in licensing and partnership agreements that contain over 200 potential milestone events and related contingent consideration. As we continue to execute our business strategy, the number of potential milestones and contingent consideration payments will only increase. As further described below, we respectfully submit that providing a detailed description of each and every potential milestone and contingent consideration for over 200 milestones will not provide our investors meaningful or material information, and will be confusing and potentially misleading to investors, primarily because:

- Disclosing all milestones and contingent consideration obscures the most important and material milestones by listing them with volumes of less material milestones and contingent consideration creating "information overload;" and
- Disclosing all milestones and contingent consideration without listing all relevant factors that may affect our receipt of the contingent consideration will lead investors to mistakenly place an unrealistic value on the revenue stream from future milestone payments, because the investor will have no information upon which to assess the likelihood of achieving each milestone i.e., the materiality of the milestone.

We propose that for each material collaboration agreement, we disclose the next potential milestone and associated contingent payment in addition to disclosing all potential milestones and contingent consideration under each agreement aggregated into the categories of development, regulatory and commercialization (as previously described in our August 12, 2011 letter). This will help investors focus on the material milestones and contingent consideration that will have the potential to impact us in the near term and thus are truly material to our business. In this way, we mitigate the risk of providing potentially confusing, misleading and non-material information to investors, while achieving the goal of plainly telling investors what is material to our business to

help them make informed investment decisions. An example of how our proposed disclosure would appear in our financial statement footnotes is attached to this letter as Attachment A.

Disclosing Every Potential Milestone Obscures the Most Important Milestones and Creates "Information Overload"

We currently disclose in the aggregate all of our milestones and related payments in our SEC reports. On an individual basis, most of our over 200 potential milestones and contingent consideration payments are not material to our business because:

- The dollar value of the contingent milestone payment is small compared to our annual total revenue;
- The probability of achieving the milestone is low; and/or
- The timing of potential achievement of the milestone is far in the future.

Therefore, listing all of these hundreds of milestones and contingent consideration payments individually would be unhelpful and potentially materially misleading to investors, because the investors would have no way to sort the material and most important milestones from the immaterial, less important milestones. This "information overload" does not achieve our mutual objective of providing meaningful material information to investors so they can make informed investment decisions.

There are numerous factors that may affect the probability and timing of when we may achieve a particular milestone and therefore receive the related contingent consideration. Each milestone has it own set of contingencies and risks. As part of our financial footnote disclosure on any milestone and contingent payment, we would need to also include information about these contingencies and risks in order to avoid potentially misleading investors. Factors that impact the probability a drug will achieve a particular milestone may include the gene target, mechanism of action, disease indication, regulatory status, clinical study design, product profile, stage of development and/or patient population. All of this additional information further compounds the problem of "information overload" and will potentially mislead investors.

In addition, each of our agreements has specific definitions for each milestone and our agreements frequently define milestone events differently. For example, an agreement may define "initiation of a phase 3 clinical trial" as occurring when the first patient is enrolled in the study, while another agreement may define "initiation of a phase 3 clinical trial" as occurring only after the first five patients are dosed with the study drug. The additional detail necessary to explain these differences would further compound the problem of "information overload" and potentially mislead investors. However, without this detail, investors may be unable to evaluate the probability and timing of achieving milestone and contingent consideration.

Further, disclosing all of our hundreds of potential milestones and contingent payments would add over 400 additional data points to the XBRL data file, which we believe would severely undermine the usefulness of such data for investors.

Disclosing All Milestones May Set Unrealistic Expectations About Future Revenues

Listing the hundreds of milestones and contingent payments under our agreements without listing each and every contingency is misleading to investors because it is an unqualified factual statement about highly contingent events. Investors may confuse these factual statements with a guarantee or promise of future revenue. Drug discovery and development is by definition experimental, and therefore inherently difficult to predict. Success depends on whether the scientific study yields the desired results. Unlike delivering a requested product, such as a number of airplanes or microchips,

achieving a drug development-related milestone does not occur simply as a function of spending time, money and/or effort. Therefore, contingent milestone payments associated with a drug's progress through development and commercialization are inherently risky and extremely difficult to predict. Neither we nor our investors can successfully "handicap" the likelihood these events will occur and, therefore, a list of individual milestone events and contingent payments creates unrealistic expectations about future revenue. Even our management, who are the best qualified to evaluate the probability of successfully achieving a milestone, has a very difficult time predicting if and when we will achieve a specified future milestone. This is particularly difficult with respect to late stage milestones associated with a drug that is in the early stage of development.

In addition, in order for investors to better evaluate the timing, likelihood and materiality of each milestone and contingent payment, we would need to provide supplemental forward looking information for each milestone and contingent payment in the financial statement footnotes. However, the purpose of the financial statement footnotes is to provide additional factual and historical detail to supplement our financial statements, and should not contain the amount and type of forward looking language necessary for investors to accurately predict when, how or if we will achieve each milestone and earn the related contingent payment under our agreements. Further, it would be too speculative for us to disclose our estimated probabilities of achieving each and every future milestone and receiving the related contingent payment in a report filed under the Exchange Act. Because independent registered public accounting firms do not possess the expertise necessary to assess the technical validity of forward

looking statements pertaining to future drug development, regulatory and commercialization activities, our independent registered public accounting firm could not independently audit such statements.

Also, as mentioned above, there are numerous factors that affect the probability that we may achieve any particular milestone and receive the related contingent consideration. As with the forward looking statements described above, these factors are not the kind of information that can be audited. Including information on the contingencies and definitions for each and every milestone and contingent payments goes well beyond the intent of the financial statement footnotes as a record of actual historical information.

An investor who has limited or no tools to appreciate and understand if or when we will ever receive the contingent milestone payments may use the unqualified list of over 200 potential milestones and contingent payments to make an unrealistic judgment about the future value of our stock and therefore make a misinformed investment decision. We respectfully submit that, given the large volume of potential milestones and contingent consideration payments in our agreements, providing a detailed description of each and every one of over 200 milestones and contingent payments increases the likelihood investors will make misinformed investment decisions, which is contrary to our and the Staff's mutual goals.

Our Proposed Disclosure Gives Investors The Information They Need To Make Infomed Investment Decisions, While Mitigating The Risk Of Confusion

We respectfully submit that our proposal to disclose the next milestone and associated contingent payment for each of our material agreements, together with the aggregated disclosure described in our previous response is more meaningful information for an investor than a detailed description of each potential milestone and its contingent consideration individually. Because the next potential milestone is closer in time, we and our investors have greater visibility regarding our progress towards achieving the milestone. As part of our disclosure in the business section of our SEC reports regarding our drug development candidates, we disclose detailed information about each of our drugs, including our plans and goals to advance each drug to the next stage of development. Many times we will also have a milestone payment under our partnered programs associated with this next stage of development. In addition, we evaluate the likelihood we will achieve the next milestone payment under each program and incorporate the results of our analyses into the financial guidance we provide our stockholders each year.

Therefore, our proposal represents more integrated disclosure of information material to investors, which will be the most meaningful and useful and not misleading to our investors because it ties together the following:

- The disclosure regarding the next potential milestone and related contingent consideration for each of our collaborations, which we will make in our financial statement footnotes;
- The progress updates we provide on our drug programs in the business section of our reports and elsewhere; and
- The periodic financial guidance we provide to our investors.

We believe this integrated approach provides our investors the right amount and type of information to make informed investment decisions without potentially misleading them. We respectfully request the Staff to consider our proposed disclosure in light of the information contained in this letter.

Substantive Milestones

As requested by the Staff, we have updated the disclosure attached to this letter as Attachment B to clarify which of our future milestones we consider to be substantive (see page B-4, lines 6-11). The attached disclosure is marked to show cumulative changes from our current disclosure.

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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 A
Proposed Disclosure

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 material 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. We will earn the next milestone payment of $XX million when the first patient is enrolled in the phase 3 clinical trial.

Attachment B
Proposed Disclosure in Significant Accounting Policies
(marked to show changes against language 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 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 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, 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. 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 determined that all future development, regulatory and commercialization milestones are substantive. For those agreements that do not meet the above 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;

- 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.