June 18, 2014

United States Securities and Exchange Commission
Division of Corporate Finance
Attn: Jeffrey P. Riedler, Assistant Director
100 F Street, NE
Washington, D.C. 20549

Re: Isis Pharmaceuticals, Inc.
Form 10-K for the Year Ended December 31, 2013
File No. 000-19125

Dear Mr. Riedler:

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 comment in reference to the Company's Form 10-K for the fiscal year ended December 31, 2013, 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.

Business
Pharmaceutical Alliances and Licensing, page 24

1. Please provide a complete discussion of all material provisions governing duration, termination, and royalty rates within a range of 10% for each of the following agreements discussed in this section:

- *the December 2012 agreement with AstraZeneca;*
- *the four separate agreements with Biogen Idec from January 2012, June 2012, December 2012 and September 2013;*
- *the March 2010 agreement with GlaxoSmithKline; and*
- *the April 2013 agreement with Roche.*

In response to the Staff's request to provide a complete discussion of all material provisions governing duration, termination and royalty rates for each of the agreements identified in the Staff's letter, we propose Isis provide the disclosure set forth on Attachment A (marked to indicate changes from language in previous Form 10-K) in Isis' future quarterly and annual reports.

* * * *

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 me at (760) 603-2732.

Sincerely,

/s/ Patrick R. O'Neil

Patrick R. O'Neil, Esq.
SVP Legal and General Counsel

Attachments:
Attachment A

AstraZeneca

In December 2012, we entered into a global collaboration agreement with AstraZeneca to discover and develop antisense drugs against five cancer targets. As part of the agreement, we granted AstraZeneca an exclusive license to develop and commercialize ISIS-STAT3Rx and ISIS-ARRx for the treatment of cancer and an option to license up to three cancer drugs under a separate research program. We are eligible to receive milestone payments and license fees from AstraZeneca as programs advance in development. In addition, we are eligible to receive ~~double digit~~ royalties up to the low to mid-teens on any product sales of drugs resulting from this collaboration. Under the terms of the agreement, we received $31 million in upfront and near-term payments comprised of a $25 million upfront payment we received in December 2012 and a $6 million payment we received in June 2013, of which we recognized $11.5 million upon receipt of the payments. We are recognizing the remaining $19.5 million as follows:

- $11.2 million related to the ISIS-ARRx program, which we are amortizing through March 2014;
- $7.6 million related to the option to license three drugs under a separate research program, which we are amortizing through December 2016; and
- $0.7 million related to the ISIS-STAT3Rx program, which we are amortizing through October 2014.

Together with AstraZeneca, we are evaluating ISIS-STAT3Rx in patients with advanced cancer. AstraZeneca is conducting a Phase 1b/2a clinical study of ISIS-STAT3Rx in patients with advanced metastatic HCC. We are concurrently completing a clinical study evaluating ISIS-STAT3Rx in patients with advanced lymphomas, including patients with diffuse large b-cell lymphoma. We are responsible for completing our clinical study in patients with advanced lymphomas and AstraZeneca is responsible for all other development activities for ISIS-STAT3Rx. In June 2013, we earned a $10 million milestone payment when AstraZeneca added a second development candidate, ISIS-ARRx, to our collaboration. If AstraZeneca successfully develops ISIS-STAT3Rx, ISIS-ARRx, and three drugs under the research program, we could receive substantive milestone payments of more than $970 million, including up to $315.5 million for the achievement of development milestones and up to $655 million for the achievement of regulatory milestones. We will earn the next milestone payment of $15 million if AstraZeneca initiates a Phase 1 study for ISIS-ARRx.

In August 2013, we added another collaboration program with AstraZeneca to discover and develop an antisense drug against an undisclosed target. AstraZeneca has the option to license a drug resulting from this research collaboration, and if AstraZeneca exercises its option, it will be responsible for all further development and commercialization of the drug. We received a $750,000 upfront payment, which we are amortizing through December 2015. We are eligible to receive license fees and substantive milestone payments of $163.2 million, including up to $45.2 million for the achievement of research and development milestones and up to $105 million for regulatory milestones. We will earn the next $3.25 million milestone payment if AstraZeneca selects a development candidate under this collaboration. In addition, we are eligible to receive ~~up to double digit~~ royalties up to the low teens on sales from any product that AstraZeneca successfully commercializes under this collaboration program.

Our agreement with AstraZeneca will continue until the expiration of all payment obligations under the agreement. In addition, the agreement, or any program under the agreement, may terminate early under the following situations:

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

During 2013 and 2012, we earned revenue of $29.1 million and $9.3 million, respectively, from our relationship with AstraZeneca, which represented 20 percent and nine percent, respectively, of our total revenue for those periods.

Biogen Idec

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

ISIS-SMNRx

In January 2012, we entered into a global collaboration agreement with Biogen Idec to develop and commercialize ISIS-SMNRx for the treatment of SMA. We received an upfront payment of $29 million, which we are amortizing through August 2016. We are eligible to receive a license fee, milestone payments and ~~up to double digit~~ royalties up to the mid-teens on any product sales of ISIS-SMNRx. Biogen Idec has the option to license ISIS-SMNRx 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.

We are evaluating ISIS-SMNRx in a Phase 2 open-label, multiple-dose, dose-escalation study in children with SMA and a Phase 2 open-label, multiple-dose, dose-escalation pilot study in infants with SMA. In January 2014, we and Biogen Idec amended the original agreement to reflect changes made to the clinical development plan for ISIS-SMNRx. We and Biogen Idec added a new open—label extension study, which is being offered to those children with SMA who have completed dosing in our previous studies, and expanded the dosing in the Phase 2 study in infants with SMA. In addition, we increased the number of patients to be included in the Phase 3 studies. As a result of these changes, we and Biogen Idec agreed to increase the payments that we are eligible to receive under this collaboration by nearly $35 million. Under the terms of the amended agreement, we are eligible to receive up to $303.8 million in a license fee and payments, including $78.8 million in milestone and other payments associated with the clinical development of ISIS-SMN Rx prior to licensing and $150 million in milestone payments if Biogen Idec achieves pre-specified regulatory milestones.

As of December 31, 2013, we had earned $7 million in milestone payments for advancing the ISIS-SMNRx Phase 2 program. In addition, based on the further advancement of ISIS-SMNRx Phase 2 program, Biogen Idec will pay us $9.3 million in the first quarter of 2014. We will earn the next milestone payment of $18 million if we dose the first patient in the Phase 3 study in infants with SMA, which is designed to support marketing registration for ISIS-SMNRx in the United States and Europe.

ISIS-DMPKRx

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 DM1, ISIS-DMPKRx. 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. Under the terms of the agreement, we received an upfront payment of $12 million, which we are amortizing through June 2017. Over the term of the collaboration we are eligible to receive up to $259 million in a license fee and substantive milestone payments. In October 2013, we earned a $10 million milestone payment when we initiated an IND-enabling toxicology study on ISIS-DMPKRx, and we are eligible to receive up to another $49 million in milestone payments associated with the development of ISIS-DMPKRx prior to licensing. We are also eligible to receive up to $130 million in milestone payments if Biogen Idec achieves pre-specified regulatory milestones. In addition, we are eligible to receive ~~up to double digit~~ royalties up to the mid-teens on any product sales of the drug. We will earn the next milestone payment of $14 million if we initiate a Phase 1 study for ISIS-DMPKRx.

Neurology

In December 2012, we and Biogen Idec entered into a third and separate collaboration to develop and commercialize novel antisense drugs to three targets to treat neurological or neuromuscular diseases. We are responsible for the development of 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, which we are amortizing through December 2020. Over the term of the collaboration we are eligible to receive up to $259 million in a license fee and substantive milestone payments per program. We could receive up to $59 million in development milestone payments to support research and development of each program, including amounts related to the cost of clinical trials, and up to $130 million in milestone payments if Biogen Idec achieves pre-specified regulatory milestones. In addition, we are eligible to receive ~~double digit~~ royalties up to the mid-teens on any product sales of drugs resulting from each of the three programs. We will earn the next milestone payment of $10 million if we initiate an IND-enabling toxicology study for a development candidate identified under this collaboration.

Strategic Neurology

In September 2013, we and Biogen Idec entered into a fourth and separate collaboration, which is a long-term strategic relationship focused on applying antisense technology to advance the treatment of neurological diseases. As part of the collaboration, Biogen Idec gained exclusive rights to the use of our antisense technology to develop therapies for neurological diseases and has the option to license drugs resulting from this collaboration. The exclusivity for neurological diseases will last six years, and may be extended for any drug development programs being pursued under the collaboration. Under the terms of the agreement, we received an upfront payment of $100 million and are eligible to receive milestone payments, license fees and royalty payments for all drugs developed through this collaboration, with the specific amounts dependent upon the modality of the molecule advanced by Biogen Idec. If we have a change of control during the first six years of the collaboration, we may be required to refund Biogen Idec a portion of the $100 million upfront payment, with the amount of the potential refund decreasing ratably as we progress through the initial six year term of the collaboration. We are amortizing the $100 million upfront payment through September 2019. Because the amortization period for the upfront payment will never be less than the initial six year term of the collaboration, the amount of revenue we recognize from the upfront payment will never exceed the amount that Biogen Idec could potentially require us to refund.

If an antisense molecule is chosen for drug discovery and development of a neurological disease, we are eligible to receive up to approximately $260 million in a license fee and substantive milestone payments for each antisense drug developed under the collaboration. We are eligible to receive up to approximately $60 million for the achievement of research and development milestones, including amounts related to the cost of clinical trials, and up to $130 million for the achievement of regulatory milestones. We will usually be responsible for drug discovery and early development of antisense drugs and Biogen Idec will have the option to license antisense drugs after Phase 2 proof of concept. Biogen Idec will then be responsible for later phase development and commercialization of the licensed drug. In addition, we are eligible to receive ~~double digit~~ royalties up to the mid-teens on any product sales of antisense drugs developed under this collaboration. If other modalities, such as small molecules or monoclonal antibodies are chosen, we are eligible to receive up to $90 million in substantive milestone payments, including up to $35 million for the achievement of research and development milestones and up to $55 million for the achievement of regulatory milestones. Biogen Idec will be responsible for all of the drug discovery and development activities for drugs using other modalities. In addition, we are eligible to receive single-digit royalties on any product sales of any drugs using other modalities developed under this collaboration. We could earn the next milestone payment of up to $10 million if we choose a target to advance under this collaboration.

Each of our agreements with Biogen Idec will continue until the earlier of the date all of Biogen Idec's options to obtain the exclusive licenses under the applicable agreement expire unexercised or, if Biogen Idec exercises its option, until the expiration of all payment obligations under the applicable agreement. In addition, each agreement, or any program under an agreement, may terminate early under the following situations:

- Biogen Idec may terminate the agreement or any program at any time by providing written notice to us;
- Under specific circumstances, if we are acquired by a third party with a product that directly competes with a compound being developed under the agreement, Biogen Idec may terminate the affected program by providing written notice to us;
- If, within a specified period of time, any required clearance of a transaction contemplated by an agreement under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, is not received, then either we or Biogen Idec may terminate the affected program by providing written notice to the other party; and
- Either we or Biogen Idec may terminate any program by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement with respect to the affected program, or the entire agreement if the other party becomes insolvent.

During 2013 and 2012, we earned revenue of $37.0 million and $8.5 million, respectively, from our relationships with Biogen Idec, which represented 25 percent and eight percent, respectively, of our total revenue for those periods.

GlaxoSmithKline

In March 2010, we entered into a strategic alliance with GSK, for up to six programs, using our antisense drug discovery platform to seek out and develop new drugs against targets for rare and serious diseases, including infectious diseases and some conditions causing blindness. This alliance allows us to control and facilitate development of drugs while still being eligible to receive milestone payments as we advance these drugs in clinical development. Under the terms of the agreement, we received a $35 million upfront payment and in May 2011 we received a $3 million payment when GSK expanded the collaboration. We are amortizing these payments through July 2015.

In October 2012, we and GSK amended the original agreement to reflect an accelerated clinical development plan for ISIS-TTRRx. Under the amended terms of the agreement, we received a $2.5 million upfront payment in December 2012, which we are amortizing through July 2015. We also received a $7.5 million milestone payment in February 2013 when we initiated the Phase 2/3 clinical study for ISIS-TTRRx and a $2 million milestone payment in December 2013 for advancing the ongoing Phase 2/3 study of ISIS-TTRRx. We have earned $24.0 million primarily in milestone payments from GSK related to the development of ISIS-TTRRx and we are eligible to earn an additional $46 million in pre-licensing milestone payments associated with the ISIS-TTRRx Phase 2/3 study. In addition, under the amended agreement, GSK increased the regulatory and commercial milestone payments we can earn should ISIS-TTRRx receive marketing approval and meet pre-agreed sales targets.

Our strategic alliance currently includes five active programs including the ISIS-TTR$_{Rx}$ program. We are eligible to receive on average up to $20 million in milestone payments through Phase 2 proof-of-concept for each program, except the ISIS-TTR$_{Rx}$ program, which we describe above. GSK has the option to license drugs from these programs at Phase 2 proof-of-concept for a license fee. If GSK exercises its option to a program it will be responsible for all further development and commercialization of the program. In September 2013, we designated ISIS-GSK3$_{Rx}$ as an additional development candidate under our collaboration with GSK. ISIS-GSK3$_{Rx}$ is an antisense drug designed to inhibit the production of an undisclosed target to treat a common viral infection. To date, we have earned $10 million in milestone payments associated with advancing the ISIS-GSK3$_{Rx}$ program including a $3 million milestone payment we earned in November 2013 when we initiated a Phase 1 study for ISIS-GSK3$_{Rx}$. In November 2013, we designated ISIS-GSK4$_{Rx}$ as an additional development candidate under our collaboration with GSK and earned a $5 million milestone payment. ISIS-GSK4$_{Rx}$ is an antisense drug we designed to treat an undisclosed ocular disease. Under our agreement, if GSK successfully develops all five programs for one or more indications and achieves pre-agreed sales targets, we could receive license fees and substantive milestone payments of nearly $1.2 billion, including up to $185.5 million for the achievement of development milestones, up to $526.5 million for the achievement of regulatory milestones and up to $445 million for the achievement of commercialization milestones. We will earn the next $1 million milestone payment if we initiate an open-label extension study of ISIS-TTR$_{Rx}$. In addition, we are eligible to receive ~~up to double digit~~ royalties up to the mid-teens on sales from any product that GSK successfully commercializes under this alliance.

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

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

During 2013, 2012 and 2011, we earned revenue of $35.3 million, $8.2 million and $17.7 million, respectively, from our relationship with GSK, which represented 24 percent, eight percent and 18 percent, respectively, of our total revenue for those years.

Roche

In April 2013, we formed an alliance with Hoffman-La Roche Inc. and F. Hoffmann-La Roche Ltd., collectively Roche, to develop treatments for Huntington's disease based on our antisense technology. Roche has the option to license the drugs from us through the completion of the first Phase 1 trial. Prior to option exercise, we are responsible for the discovery and development of an antisense drug targeting huntingtin, or HTT, protein. We are also working collaboratively with Roche on the discovery of an antisense drug utilizing Roche's "brain shuttle" program. If Roche exercises its option, it will be responsible for global development, regulatory and commercialization activities for any drug arising out of the collaboration. Under the terms of the agreement, we received an upfront payment of $30 million in April 2013, which we are amortizing through April 2017. We are eligible to receive up to $362 million in a license fee and substantive milestone payments including up to $67 million for the achievement of development milestones, up to $170 million for the achievement of regulatory milestones and up to $80 million for the achievement of commercialization milestones. In addition, we are eligible to receive up to $136.5 million in milestone payments for each additional drug successfully developed and up to $50 million in commercial milestones if a drug using Roche's proprietary brain shuttle technology is successfully commercialized. We are also eligible to receive tiered royalties up to the mid-teens on any product sales of drugs resulting from this alliance. We will earn the next milestone payment of $22 million if we initiate a Phase 1 trial for a drug targeting HTT protein.

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

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

During 2013, we earned revenue of $5.1 million from our relationship with Roche.