



DIVISION OF
CORPORATION FINANCE

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

June 4, 2014

Via E-mail

Patrick R. O'Neil, Esq.
Senior Vice President and General Counsel
Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010

**Re: Isis Pharmaceuticals, Inc.
Form 10-K for the Fiscal year Ended December 31, 2013
Filed March 3, 2014
File No. 000-19125**

Dear Mr. O'Neil:

We have reviewed your filing and have the following comment. In our comment, we may ask you to provide us with information so we may better understand your disclosure.

Please respond to this letter within 10 business days by providing the requested information or by advising us when you will provide the requested response. If you do not believe our comment applies to your facts and circumstances, please tell us why in your response.

After reviewing the information you provide in response to this comment, we may have additional comments.

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.

We urge all persons who are responsible for the accuracy and adequacy of the disclosure in the filing to be certain that the filing includes all information the Securities Exchange Act of 1934 and all applicable Exchange Act rules require. Since the company and its management are

Patrick R. O'Neil, Esq.
Isis Pharmaceuticals, Inc.
June 4, 2014
Page 2

in possession of all facts relating to a company's disclosure, they are responsible for the accuracy and adequacy of the disclosures they have made.

In responding to our comment, please provide a written statement from the company acknowledging that:

- the company is responsible for the adequacy and accuracy of the disclosure in the filing;
- staff comments or changes to disclosure in response to staff comments do not foreclose the Commission from taking any action with respect to the filing; 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.

Please contact Austin Stephenson at (202) 551-3192 or me at (202) 551-3715 with any questions.

Sincerely,

/s/ Jeffrey P. Riedler

Jeffrey P. Riedler
Assistant Director