

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

CURRENT REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

Date of report (Date of earliest event reported): March 1, 2007

ISIS PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Charter)

Delaware

(State or Other Jurisdiction of Incorporation)

000-19125

(Commission File No.)

33-0336973

(IRS Employer Identification No.)

1896 Rutherford Road
Carlsbad, CA 92008

(Address of Principal Executive Offices and Zip Code)

Registrant's telephone number, including area code: (760) 931-9200

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

- Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
- Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
- Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
- Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Item 1.01. Entry into a Material Definitive Agreement.

Isis Pharmaceuticals, Inc. ("Isis") recently recruited Jeff Jonas, MD as Executive Vice President responsible for development, to whom Dr. Mark K. Wedel now reports. To affirm its commitment to Dr. Wedel as a senior contributor to Isis long term and to assure effective integration of Dr. Jonas, Isis entered an employee retention agreement with Dr. Wedel, a copy of which is attached to this Report as Exhibit 10.1 (the "Employment Agreement").

Although Isis does not generally enter formal employment agreements with its employees, Isis designed the Employment Agreement in recognition of the significant change represented by the recruitment of Dr. Jonas and to present Dr. Wedel with an opportunity to contribute as an Isis employee for the long term. However, should Dr. Wedel decide the change is unsatisfactory, he may resign, and may be eligible to receive a salary continuation benefit depending on the date of his termination. If Dr. Wedel remains an employee of Isis through June 1, 2007, he will be eligible to receive a salary continuation benefit equal to 12 months plus two additional months of salary continuation for every month he remains an employee after June 1, 2007, not to exceed a maximum of 18 months salary continuation.

The description of the Employment Agreement set forth above is qualified in its entirety by reference to the full and complete terms set forth in such agreement filed as an exhibit to this Report and incorporated by reference herein.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits.

10.1 Employment Agreement dated March 1, 2007 between Isis and Mark K. Wedel.

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Isis Pharmaceuticals, Inc.

Dated: March 5, 2007

By: /s/ B. Lynne Parshall

B.LYNNE PARSHALL

Executive Vice President,

Chief Financial Officer and Director

March 1, 2007

Dear Mark:

I am pleased to confirm in writing our conversation of January 29. It remains very much my desire to have you continue to be a senior leader at Isis for the long term. However, I do understand that you view the recruitment of Jeff Jonas as a significant change and one that you may need some time with which to become comfortable. As you know, the Board and I view the addition of Jeff to the development organization as a natural and important organizational evolution and we are very supportive of you and your continuing role at Isis. I hope you will agree. Moreover, I believe it is very much in your interest, the interest of ISIS 301012, our pipeline, your organization, and Isis for you to remain at Isis and for you to develop a successful long term working relationship with Jeff, or at worst to assure an effective transition.

We therefore have agreed that you will continue to work for Isis in your current capacity for at least six to nine months beginning February 1, 2007. I am hopeful that you will be here for the long term. During the next six to nine months time you will assure continued development of ISIS 301012, the pipeline, and your organization and an effective transition for Jeff. If you conclude that you prefer to depart from Isis, you will inform Jeff and me two months in advance of your planned departure date, in other words, you will inform us of your plans to leave between June 1 and August 1, 2007. If you choose to leave and so inform us in writing, Isis will provide salary continuation for two times the number of months you have worked during this transition period (12-18 months).

During salary continuation, you will receive your salary and benefits. You will not be eligible for bonuses or stock option grants. Your accrued vacation time will be used during your time out of the office. Salary continuation will terminate when you (1) accept another job, (2) accept a consulting relationship, (3) accept a position on a board of directors, (4) practice medicine, or (5) in any other way are compensated for your services. If you choose this option we will document it with a Termination and Release Agreement.

In closing, Mark, let me reiterate that I am optimistic that you will not choose to exercise this option and that I appreciate your commitment to trying to assure that this agreement never needs to be exercised.

Regards,

/s/ Stan Crooke

Stan Crooke

/s/ Mark Wedel

Mark Wedel

cc: Lynne Parshall
