

INITIAL STATEMENT OF BENEFICIAL OWNERSHIP OF SECURITIES

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934 or Section 30(h) of the Investment Company Act of 1940

| OMB APPROVAL                                 |           |
|--|-----------|
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|  |         |          |   |  |   |  |  |
|--|---------|----------|---|--|---|--|--|
| 1. Name and Address of Reporting Person*<br><b>O'NEIL PATRICK R.</b> |         |          | 2. Date of Event Requiring Statement (Month/Day/Year)<br><b>01/01/2013</b>  |  | 3. Issuer Name and Ticker or Trading Symbol<br><b>ISIS PHARMACEUTICALS INC [ ISIS ]</b> |  |  |
| (Last)   | (First) | (Middle) | 4. Relationship of Reporting Person(s) to Issuer (Check all applicable)<br>Director _____ 10% Owner _____<br><b>X</b> Officer (give title below) _____ Other (specify below) _____<br><b>SVP, Legal and General Counsel</b> |  |   | 5. If Amendment, Date of Original Filed (Month/Day/Year)   |  |
| C/P ISIS PHARMACEUTICALS, INC.<br>2855 GAZELLE COURT                 |         |          |   |  |   | 6. Individual or Joint/Group Filing (Check Applicable Line)<br><b>X</b> Form filed by One Reporting Person<br>Form filed by More than One Reporting Person |  |
| (Street)   | (City)  | (State)  | (Zip)   |  |   |  |  |
| CARLSBAD   | CA      | 92010    |   |  |   |  |  |

Table I - Non-Derivative Securities Beneficially Owned

| 1. Title of Security (Instr. 4) | 2. Amount of Securities Beneficially Owned (Instr. 4) | 3. Ownership Form: Direct (D) or Indirect (I) (Instr. 5) | 4. Nature of Indirect Beneficial Ownership (Instr. 5) |
|---------------------------------|---|--|---|
| Common Stock                    | 2,328   | D  |   |

Table II - Derivative Securities Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)

| 1. Title of Derivative Security (Instr. 4) | 2. Date Exercisable and Expiration Date (Month/Day/Year) |                 | 3. Title and Amount of Securities Underlying Derivative Security (Instr. 4) |                            | 4. Conversion or Exercise Price of Derivative Security | 5. Ownership Form: Direct (D) or Indirect (I) (Instr. 5) | 6. Nature of Indirect Beneficial Ownership (Instr. 5) |
|--|--|-----------------|---|----------------------------|--|--|---|
|  | Date Exercisable   | Expiration Date | Title   | Amount or Number of Shares |  |  |   |
| Employee Stock Option (right to buy)       | 01/02/2011   | 01/01/2014      | Common Stock  | 1,350                      | 11.12  | D  |   |
| Employee Stock Option (right to buy)       | 01/02/2012   | 01/01/2015      | Common Stock  | 14,000                     | 15.38  | D  |   |
| Employee Stock Option (right to buy)       | 01/01/2013   | 12/31/2015      | Common Stock  | 25,000                     | 14.18  | D  |   |
| Employee Stock Option (right to buy)       | (1)  | 01/01/2016      | Common Stock  | 9,400                      | 14.47  | D  |   |
| Employee Stock Option (right to buy)       | (2)  | 01/03/2017      | Common Stock  | 17,400                     | 11.27  | D  |   |
| Employee Stock Option (right to buy)       | (3)  | 08/31/2017      | Common Stock  | 6,700                      | 8  | D  |   |
| Employee Stock Option (right to buy)       | (4)  | 01/02/2018      | Common Stock  | 19,000                     | 10.29  | D  |   |
| Employee Stock Option (right to buy)       | (5)  | 01/02/2019      | Common Stock  | 19,500                     | 7.25   | D  |   |
| Restricted Stock Unit                      | (6)  | (6)             | Common Stock  | 2,166                      | (7)  | D  |   |

Explanation of Responses:

- Grant of 1/2/09 to reporting person of stock options under the Isis Pharmaceuticals, Inc. 1989 Stock Option Plan. 25% of the shares subject to the option vested and became exercisable on 1/2/10. Thereafter, the remaining shares subject to the option vested and became exercisable in 36 equal monthly installments, at the rate of 2,350 shares per year. The option is exercisable as to 9,204 on 1/1/13.
- Grant of 1/4/10 to reporting person of stock options under the Isis Pharmaceuticals, Inc. 1989 Stock Option Plan. 25% of the shares subject to the option vested and became exercisable on 1/4/11. Thereafter, the remaining shares subject to the option vested and became exercisable in 36 equal monthly installments, at the rate of 4,350 shares per year. The option is exercisable as to 12,687 on 1/1/13.
- Grant of 9/1/10 to reporting person of stock options under the Isis Pharmaceuticals, Inc. 1989 Stock Option Plan. 25% of the shares subject to the option vested and became exercisable on 9/1/11. Thereafter, the remaining shares subject to the option vested and became exercisable in 36 equal monthly installments, at the rate of 2,500 shares per year. The option is exercisable as to 2,533 on 1/1/13. SAY SOMETHING ABOUT OPTIONS ALREADY EXERCISED????
- Grant of 1/3/11 to reporting person of stock options under the Isis Pharmaceuticals, Inc. 1989 Stock Option Plan. 25% of the shares subject to the option vested and became exercisable on 1/3/12. Thereafter, the remaining shares subject to the option vested and became exercisable in 36 equal monthly installments, at the rate of 5,750 shares per year. The option is exercisable as to 7,020 on 1/1/13. SAY SOMETHING ABOUT OPTIONS ALREADY EXERCISED????
- Grant of 1/3/12 to reporting person of stock options under the Isis Pharmaceuticals, Inc. 1989 Stock Option Plan. 25% of the shares subject to the option vested and became exercisable on 1/3/13. Thereafter, the remaining shares subject to the option vested and became exercisable in 36 equal monthly installments, at the rate of 4,875 shares per year. The option is exercisable as to 0 on 1/1/13.
- The restricted stock units vest in four equal annual installments, the first installment vesting on January 15, 2013. Upon vesting, the restricted stock units will be paid out in whole shares of Isis common stock or cash as may be determined by the Company. The RSU shall be fully vested on January 15, 2016. The RSU is vested as to 0 shares on January 1, 2012.
- Each restricted stock unit represents a contingent right to receive one share of Isis common stock or its equivalent cash value.

Remarks:

/s/Patrick O'Neil

\*\* Signature of Reporting Person

01/03/2013

Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see instruction 5 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see instruction 6 for procedure.

Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.

POWER OF ATTORNEY

Know all by these presents, that the undersigned hereby constitutes and appoints each of Stanley T. Crooke and B. Lynne Parshall, signing individually, the undersigned (1) execute for and on behalf of the undersigned, an officer, director or holder of 10% or more of a registered class of securities of Isis Pharmaceuticals, Inc. (Isis), (2) do and perform any and all acts for and on behalf of the undersigned that may be necessary or desirable to complete and execute such Form 3, 4 or 5, complete and file such Form 3, 4 or 5, (3) take any other action of any nature whatsoever in connection with the foregoing which, in the opinion of such attorney-in-fact, may be of benefit, in the best interest of Isis. The undersigned hereby grants to each such attorney-in-fact full power and authority to do and perform any and every act and thing whatsoever requisite, necessary, convenient or proper in the premises, and which may in anywise relate to the foregoing, and to execute and file the same, and to do and perform any and every act and thing whatsoever requisite, necessary, convenient or proper in the premises, and which may in anywise relate to the foregoing, and to execute and file the same, and to do and perform any and every act and thing whatsoever requisite, necessary, convenient or proper in the premises, and which may in anywise relate to the foregoing, and to execute and file the same. This Power of Attorney shall remain in full force and effect until the earliest to occur of (a) the undersigned is no longer required to file Forms 3, 4 and 5 with the SEC.

IN WITNESS WHEREOF, the undersigned has caused this Power of Attorney to be executed as of this 1st day of January, 2013.

/S/Patrick R. O'Neil