

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><u>Monia Brett P</u><br><br>(Last) (First) (Middle)<br>C/O ISIS PHARMACEUTICALS, INC.<br>2855 GAZELLE COURT<br><br>(Street)<br>CARLSBAD CA 92010<br><br>(City) (State) (Zip) | 2. Date of Event Requiring Statement (Month/Day/Year)<br>12/01/2011 | 3. Issuer Name and Ticker or Trading Symbol<br><u>ISIS PHARMACEUTICALS INC [ ISIS ]</u>  | 5. If Amendment, Date of Original Filed (Month/Day/Year)  |
|  |   | 4. Relationship of Reporting Person(s) to Issuer (Check all applicable)<br>Director 10% Owner<br><input checked="" type="checkbox"/> Officer (give title below) Other (specify below)<br>Senior Vice President | 6. Individual or Joint/Group Filing (Check Applicable Line)<br><input checked="" type="checkbox"/> Form filed by One Reporting Person<br>Form filed by More than One Reporting Person |

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                    | 5,073   | 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 |   |  |  |   |
| Employee Stock Option (right to buy)       | 01/02/2008   | 01/01/2014      | Common Stock 18,240   | 6.81   | D  |   |
| Employee Stock Option (right to buy)       | 01/03/2010   | 01/02/2013      | Common Stock 12,031   | 5.25   | D  |   |
| Employee Stock Option (right to buy)       | 01/02/2011   | 01/01/2014      | Common Stock 19,500   | 11.12  | D  |   |
| Employee Stock Option (right to buy)       | 01/01/2012   | 12/31/2014      | Common Stock 10,000   | 15.75  | D  |   |
| Employee Stock Option (right to buy)       | 01/02/2012 <sup>(1)</sup>                                | 01/01/2015      | Common Stock 20,000   | 15.38  | D  |   |
| Employee Stock Option (right to buy)       | 01/02/2010 <sup>(2)</sup>                                | 01/01/2016      | Common Stock 22,500   | 14.47  | D  |   |
| Employee Stock Option (right to buy)       | 02/16/2010 <sup>(3)</sup>                                | 02/15/2016      | Common Stock 5,000  | 14.65  | D  |   |
| Employee Stock Option (right to buy)       | 01/04/2011 <sup>(4)</sup>                                | 01/03/2017      | Common Stock 22,500   | 11.27  | D  |   |
| Employee Stock Option (right to buy)       | 01/03/2012 <sup>(5)</sup>                                | 01/02/2018      | Common Stock 22,600   | 10.29  | D  |   |

Explanation of Responses:

- Grant of 1/2/08 to reporting person of stock options under the Isis Pharmaceuticals, Inc. 2000 Broad-Based Equity Incentive Plan. 25% of the shares subject to the option vested and became exercisable on 1/2/09. Thereafter, the remaining shares subject to the option vested and became exercisable in 36 equal monthly installments, at the rate of 5,000 shares per year. The option is exercisable as to 19,583 shares on 1/1/12.
- 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 5,625 shares per year. The option is exercisable as to 16,406 shares on 1/1/12.
- Grant of 2/16/09 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 2/16/10. Thereafter, the remaining shares subject to the option vested and became exercisable in 36 equal monthly installments, at the rate of 1,250 shares per year. The option is exercisable as to 3,541 shares on 1/1/12.
- 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 5,625 shares per year. The option is exercisable as to 10,781 shares on 1/1/12.
- 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 will vest and become exercisable on 1/3/12. Thereafter, the remaining shares subject to the option vest and become exercisable in 36 equal monthly installments, at the rate of 5,650 shares per year. The option is exercisable as to 0 shares on 1/1/12.

Remarks:

/s/B. Lynne Parshall, Attorney-In-Fact

01/03/2012

\*\* Signature of Reporting Person

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 the undersigned might lawfully do or perform in person. 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, 2012.

/S/Brett P. Monia