

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

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

1. Name and Address of Reporting Person* <u>O'NEIL PATRICK R.</u>  (Last) (First) (Middle) <u>C/O ISIS PHARMACEUTICALS, INC.</u> <u>2855 GAZELLE COURT</u>  (Street) <u>CARLSBAD CA 92010</u>  (City) (State) (Zip)	2. Issuer Name and Ticker or Trading Symbol <u>ISIS PHARMACEUTICALS INC [ ISIS ]</u>  3. Date of Earliest Transaction (Month/Day/Year) <u>01/15/2014</u>  4. If Amendment, Date of Original Filed (Month/Day/Year)	5. Relationship of Reporting Person(s) to Issuer (Check all applicable) Director 10% Owner X Officer (give title below) Other (specify below) <u>SVP, Legal &amp; General Counsel</u>  6. Individual or Joint/Group Filing (Check Applicable Line) X Form filed by One Reporting Person Form filed by More than One Reporting Person
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**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	01/15/2014	01/15/2014	M <sup>(1)</sup>		654 <sup>(1)</sup>	A	\$0	3,072	D	
Common Stock	01/16/2014	01/16/2014	S <sup>(2)</sup>		250 <sup>(2)</sup>	D	\$47.0812	2,822	D	
Common Stock	01/15/2014	01/15/2014	M <sup>(3)</sup>		542 <sup>(3)</sup>	A	\$0	3,364	D	
Common Stock	01/16/2014	01/16/2014	S <sup>(4)</sup>		207 <sup>(4)</sup>	D	\$47.081	3,157	D	
Common Stock	01/15/2014	01/15/2014	M <sup>(1)</sup>		313 <sup>(1)</sup>	A	\$0	3,470	D	
Common Stock	01/16/2014	01/16/2014	S <sup>(2)</sup>		120 <sup>(2)</sup>	D	\$47.0812	3,350	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)	
				Code	V	(A)	(D)	Date Exercisable	Expiration Date						Title
Restricted Stock Units	(5)	01/15/2014	01/15/2014	A		7,500		(6)	(6)	Common Stock	7,500	\$0	7,500	D	
Restricted Stock Units	(5)	01/15/2014	01/15/2014	M			654 <sup>(2)</sup>	(7)	(7)	Common Stock	654	\$0	1,961	D	
Restricted Stock Units	(5)	01/15/2014	01/15/2014	M			542 <sup>(4)</sup>	(8)	(8)	Common Stock	542	\$0	1,082	D	
Restricted Stock Units	(5)	01/15/2014	01/15/2014	M			313 <sup>(2)</sup>	(7)	(7)	Common Stock	313	\$0	937	D	

**Explanation of Responses:**

- Acquired pursuant to vesting and release of shares pursuant to an RSU award granted on January 15, 2013.
- The sale was made pursuant to an automatic sale to cover the required tax withholding obligations pursuant to the 2011 Equity Incentive Plan Restricted Stock Unit Agreement and Grant Notice, dated January 15, 2013.
- Acquired pursuant to vesting and release of shares pursuant to an RSU award granted on January 15, 2012.
- The sale was made pursuant to an automatic sale to cover the required tax withholding obligations pursuant to the 2011 Equity Incentive Plan Restricted Stock Unit Agreement and Grant Notice, dated January 15, 2012.
- Each Restricted Stock Unit represents a contingent right to receive one share of Isis common stock, or its equivalent cash value.
- Grant 1/15/2014 to reporting person of Restricted Stock Units under the Isis Pharmaceuticals, Inc. 2011 Equity Incentive Plan. Restricted Stock Units vest in four equal annual installments, the first installment vesting on January 15, 2015. 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 vest on January 15, 2018. The RSU is vested as to 0 shares on January 15, 2014.
- Restricted Stock Unit Award granted on January 15, 2013. Restricted Stock Units vest in equal annual installments, the first installment vested on January 15, 2014. 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, 2017.
- Restricted Stock Unit Award granted on January 15, 2012. Restricted Stock Units vest in equal annual installments, the first installment vested 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.

**Remarks:**

/s/Patrick R. O'Neil

01/17/2014

\*\* 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 4 (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.**