

**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

OMB APPROVAL	
OMB Number:	3235-0287
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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>	5. Relationship of Reporting Person(s) to Issuer (Check all applicable)  Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) <u>SVP, Legal &amp; General Counsel</u>
	3. Date of Earliest Transaction (Month/Day/Year) <u>07/01/2014</u>	
		6. Individual or Joint/Group Filing (Check Applicable Line)  <input checked="" type="checkbox"/> Form filed by One Reporting Person <input type="checkbox"/> Form filed by More than One Reporting Person

**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	07/01/2014	07/01/2014	J <sup>(1)</sup>	V	403	A	\$30.2005	3,753	D	
Common Stock	07/01/2014	07/01/2014	M <sup>(2)</sup>		1,500 <sup>(2)</sup>	A	\$10.29	5,253	D	
Common Stock	07/01/2014	07/01/2014	S <sup>(2)</sup>		1,500 <sup>(3)</sup>	D	\$35.3333	3,753	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					
Employee Stock Option (right to buy)	\$10.29	07/01/2014	07/01/2014	M			1,500	01/03/2015 <sup>(4)</sup>	01/02/2018	Common Stock	\$0	8,983	D	

**Explanation of Responses:**

- Reporting 403 shares acquired under the Isis Pharmaceuticals, Inc. Amended and Restated 2000 Employee Stock Purchase Plan on July 1, 2014. These 403 shares may not be sold until January 2, 2015.
- Acquired as a result of exercising a stock option pursuant to Rule 10b5-1 Trading Plan. The purchase and sale reported on this Form 4 was effective pursuant to Rule 10b5-1 Trading Plans adopted by the reporting person on 1/2/14.
- The price reported in Column 4 is a weighted average price. These shares were sold in multiple transactions at prices ranging from \$35.20 to \$35.50, inclusive. The reporting person undertakes to provide to Isis Pharmaceuticals, Inc., any security holder of Isis Pharmaceuticals, Inc. or the staff of the Securities and Exchange Commission, upon request, full information regarding the number of shares sold at each separate price within the ranges set forth in footnote (3) on this Form 4.
- Grant of 1/3/2011 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 1/3/2012. Thereafter, the remaining shares subject to the option vest and become exercisable in 36 equal monthly installments, at the rate of 5,750 shares per year. Following this transaction, the option was exercisable as to 5,628 on 7/1/2014.

**Remarks:**

/s/Patrick R. O'Neil 07/02/2014  
 \*\* 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.