

**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) C/O ISIS PHARMACEUTICALS, INC. 2855 GAZELLE COURT  (Street) CARLSBAD CA 92010  (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>03/19/2015</u>	
	4. If Amendment, Date of Original Filed (Month/Day/Year)	
		6. Individual or Joint/Group Filing (Check Applicable Line) <input checked="" type="checkbox"/> Form filed by One Reporting Person 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	03/19/2015	03/19/2015	M <sup>(1)</sup>		1,617 <sup>(1)</sup>	A	\$10.29	7,791	D	
Common Stock	03/19/2015	03/19/2015	S <sup>(1)</sup>		1,617 <sup>(1)</sup>	D	\$74.767	6,174	D	
Common Stock	03/19/2015	03/19/2015	M <sup>(1)</sup>		5,683 <sup>(1)</sup>	A	\$7.25	11,857	D	
Common Stock	03/19/2015	03/19/2015	S <sup>(1)</sup>		5,683 <sup>(1)</sup>	D	\$74.767	6,174	D	
Common Stock	03/19/2015	03/19/2015	M <sup>(1)</sup>		6,100 <sup>(1)</sup>	A	\$10.82	12,274	D	
Common Stock	03/19/2015	03/19/2015	S <sup>(1)</sup>		6,100 <sup>(1)</sup>	D	\$74.767	6,174	D	
Common Stock	03/19/2015	03/19/2015	M <sup>(1)</sup>		4,000 <sup>(1)</sup>	A	\$10.82	10,174	D	
Common Stock	03/19/2015	03/19/2015	S <sup>(1)</sup>		4,000 <sup>(1)</sup>	D	\$74.767	6,174	D	
Common Stock	03/19/2015	03/19/2015	M <sup>(1)</sup>		2,600 <sup>(1)</sup>	A	\$39.87	8,774	D	
Common Stock	03/19/2015	03/19/2015	S <sup>(1)</sup>		2,600 <sup>(1)</sup>	D	\$74.767	6,174	D	
Common Stock	03/19/2015	03/19/2015	M <sup>(1)</sup>		10,525 <sup>(1)</sup>	A	\$39.87	16,699	D	
Common Stock	03/19/2015	03/19/2015	S <sup>(1)</sup>		10,525 <sup>(1)</sup>	D	\$75.004	6,174	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	Amount or Number of Shares				
Employee Stock Option (right to buy)	\$10.29	03/19/2015	03/19/2015	M			1,617	01/03/2015	01/02/2018	Common Stock	1,617	\$0	0	D	
Employee Stock Option (right to buy)	\$7.25	03/19/2015	03/19/2015	M			5,683	01/03/2013 <sup>(2)</sup>	01/02/2019	Common Stock	5,683	\$0	4,067	D	
Employee Stock Option (right to buy)	\$10.82	03/19/2015	03/19/2015	M			6,100	01/02/2014 <sup>(3)</sup>	01/01/2020	Common Stock	6,100	\$0	7,253	D	
Employee Stock Option (right to buy)	\$10.82	03/19/2015	03/19/2015	M			4,000	01/02/2014 <sup>(4)</sup>	01/01/2020	Common Stock	4,000	\$0	3,500	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	Amount or Number of Shares				
Employee Stock Option (right to buy)	\$39.87	03/19/2015	03/19/2015	M			13,125	01/02/2015 <sup>(5)</sup>	01/01/2021	Common Stock	13,125	\$0	31,875	D	

**Explanation of Responses:**

1. 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 Plan adopted by the reporting person on 2/3/2015.
2. Grant of 1/3/2012 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 1/3/2013. Thereafter, the remaining shares subject to the option vest and become exercisable in 36 equal monthly installments, at the rate of 4,875 shares per year. Following this transaction, the option was exercisable as to 4 on 3/19/2015.
3. Grant of 1/2/2013 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 1/2/2014. Thereafter, the remaining shares subject to the option vest and become exercisable in 36 equal monthly installments, at the rate of 3,925 shares per year. Following this transaction, the option was exercisable as to 57 on 3/19/2015.
4. Grant of 1/2/2013 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 1/2/2014. Thereafter, the remaining shares subject to the option vest and become exercisable in 36 equal monthly installments, at the rate of 1,875 shares per year. Following this transaction, the option was exercisable as to 62 on 3/19/2015.
5. Grant of 1/2/2014 to reporting person of stock options under the Isis Pharmaceuticals, Inc. 2011 Equity Incentive Plan. 25% of the shares subject to the option vest and become exercisable on 1/2/2015. Thereafter, the remaining shares subject to the option vest and become exercisable in 36 equal monthly installments, at the rate of 11,250 shares per year. Following this transaction, the option was exercisable as to 0 on 3/19/2015.

**Remarks:**

/s/Patrick R. O'Neil

03/20/2015

\*\* 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.

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