

STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

OMB APPROVAL	
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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* O'NEIL PATRICK R.			2. Issuer Name and Ticker or Trading Symbol ISIS PHARMACEUTICALS INC [ISIS]			5. Relationship of Reporting Person(s) to Issuer (Check all applicable) Director <input type="checkbox"/> 10% Owner <input type="checkbox"/> Officer (give title below) <input checked="" type="checkbox"/> SVP, Legal & General Counsel		
(Last) (First) (Middle) C/O ISIS PHARMACEUTICALS, INC. 2855 GAZELLE COURT			3. Date of Earliest Transaction (Month/Day/Year) 01/01/2015					
(Street) CARLSBAD CA 92010			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 <input type="checkbox"/> Form filed by More than One Reporting Person		
(City) (State) (Zip)								

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	01/01/2015	01/01/2015	j ⁽⁴⁾	v	329	A	\$30.0475	4,082	D	
Common Stock	01/02/2015	01/02/2015	m ⁽²⁾		1,217 ⁽²⁾	A	\$10.82	5,299	D	
Common Stock	01/02/2015	01/02/2015	s ⁽²⁾		1,217 ⁽²⁾	D	\$62.115	4,082	D	
Common Stock	01/02/2015	01/02/2015	m ⁽²⁾		283 ⁽²⁾	A	\$7.25	4,365	D	
Common Stock	01/02/2015	01/02/2015	s ⁽²⁾		283 ⁽²⁾	D	\$62.115	4,082	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)	\$61.57	01/02/2015	01/02/2015	A		31,457		01/02/2016 ⁽³⁾	01/01/2022	Common Stock	31,457	\$0	31,457	D	
Employee Stock Option (right to buy)	\$10.82	01/02/2015	01/02/2015	M			1,217	01/02/2014 ⁽⁴⁾	01/01/2020	Common Stock	1,217	\$0	13,353	D	
Employee Stock Option (right to buy)	\$7.25	01/02/2015	01/02/2015	M			283	01/03/2013 ⁽⁵⁾	01/02/2019	Common Stock	283	\$0	9,750	D	

Explanation of Responses:

- Reporting 329 shares acquired under the Isis Pharmaceuticals, Inc. Amended and Restated 2000 Employee Stock Purchase Plan on January 1, 2015. These 329 shares may not be sold until July 2, 2015.
- Acquired as a result of exercising a stock option pursuant to a Rule 10b5-1 Trading Plan. The purchase and sale reported on this Form 4 was effective pursuant to a Rule 10b5-1 Trading Plan adopted by the reporting person on 1/2/2014.
- Grant of 1/2/2015 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 1/2/2016. Thereafter, the remaining shares subject to the option vest and become exercisable in 36 equal monthly installments, at the rate of 7,865 shares per year. The option was exercisable as to 0 on 1/2/2015.
- 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 become 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 5,503 on 1/2/2015.
- 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 become 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 4,468 on 1/2/2015.

Remarks:

/s/Patrick R. O'Neil

01/05/2015

** 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.

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, and (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, and proper to carry out the powers and authority herein granted. 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