

OMB APPROVAL	
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**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/P 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 and General Counsel</u>
	3. Date of Earliest Transaction (Month/Day/Year) <u>01/01/2013</u>	
4. If Amendment, Date of Original Filed (Month/Day/Year)		

**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	01/01/2013	01/01/2013	J <sup>(1)</sup>	v	431 <sup>(1)</sup>	A	\$8.874	2,759	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
Employee Stock Option (right to buy)	\$10.82	01/02/2013	01/02/2013	A		7,500		(2)	01/01/2020	Common Stock	7,500	\$0	7,500	D	
Employee Stock Option (right to buy)	\$10.82	01/02/2013	01/02/2013	A		15,700		(3)	01/01/2020	Common Stock	15,700	\$0	15,700	D	

**Explanation of Responses:**

- Reporting 431 shares acquired under the Isis Pharmaceuticals, Inc. Amended and Restated 2000 Employee Stock Purchase Plan on January 1, 2013. These 431 shares may not be sold until July 2, 2013.
- Grant of 1/2/13 to reporting person of stock options under the Isis Pharmaceuticals, Inc. 1989 Stock Option Plan. 25% of the shares subject to the option vest and become exercisable on 1/2/14. 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. The option is exercisable as to 0 on 1/2/13.
- Grant of 1/2/13 to reporting person of stock options under the Isis Pharmaceuticals, Inc. 1989 Stock Option Plan. 25% of the shares subject to the option vest and become exercisable on 1/2/14. 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. The option is exercisable as to 0 on 1/2/13.

**Remarks:**

/s/Patrick R. O'Neil 01/03/2013  
 \*\* 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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