

**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>LOSCALZO JOSEPH</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) <input checked="" type="checkbox"/> Director 10% Owner  Officer (give title below) Other (specify below)
	3. Date of Earliest Transaction (Month/Day/Year) <u>07/01/2014</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			

**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	(1)	07/01/2014	07/01/2014	A		2,667		(2)	(2)	Common Stock	2,667	\$0	2,667	D	
Director Stock Option (right to buy)	\$35.53	07/01/2014	07/01/2014	A		16,000		07/01/2015 <sup>(3)</sup>	06/30/2024	Common Stock	16,000	\$0	16,000	D	

**Explanation of Responses:**

- Each Restricted Stock Unit represents a contingent right to receive one share of Isis common stock, or its equivalent cash value.
- Grant of July 1, 2014 to reporting person of stock options under the Amended and Restated Isis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan. The option vests and becomes exercisable in four equal annual installments, the first installment vesting on July 1, 2015. The option shall be fully vested and exercisable on July 1, 2018. The option is exercisable as to 0 shares on July 1, 2014.
- Grant of July 1, 2014 to reporting person of stock options under the Amended and Restated Isis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan. The option vests and becomes exercisable in four equal annual installments, the first installment vesting on July 1, 2015. The option shall be fully vested and exercisable on July 1, 2018. The option is exercisable as to 0 shares on July 1, 2014.

**Remarks:**

/s/B. Lynne Parshall, attorney- 07/02/2014  
in-fact

\*\* 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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