

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>KLEIN JOSEPH III</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>11/11/2015</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	11/11/2015	11/11/2015	M ⁽¹⁾		3,750 ⁽¹⁾	A	\$9.3	9,293	D	
Common Stock	11/11/2015	11/11/2015	S ⁽²⁾		3,750 ⁽²⁾	D	\$64.1795 ⁽³⁾	5,543	D	
Common Stock	11/11/2015	11/11/2015	M ⁽¹⁾		3,125 ⁽¹⁾	A	\$12.94	8,668	D	
Common Stock	11/11/2015	11/11/2015	S ⁽²⁾		3,125 ⁽²⁾	D	\$64.1795 ⁽³⁾	5,543	D	
Common Stock								100	I	By Son

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
Director Stock Option (right to buy)	\$9.3	11/11/2015	11/11/2015	M			3,750	07/01/2015	06/30/2021	Common Stock	3,750	\$0	0	D	
Director Stock Option (right to buy)	\$12.94	11/11/2015	11/11/2015	M			3,125	07/02/2013 ⁽⁴⁾	07/01/2022	Common Stock	3,125	\$0	2,812	D	

Explanation of Responses:

- Acquired as a result of exercising a stock option.
- The sale was made pursuant to shares owned.
- The price reported in Column 4 is a weighted average price. These shares were sold in multiple transactions at prices ranging from \$64.03 to \$64.44, 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 7/2/2012 to reporting person of stock options under the Isis Pharmaceuticals, Inc. Amended & Restated 2002 Non-Employee Directors' Stock Option Plan. The option vests and becomes exercisable in four equal annual installments, the first installment vesting on 7/2/2013. The option shall be fully vested and exercisable on 7/2/2016. Following this transaction, the stock option was exercisable as to 0 shares on 11/11/2015.

Remarks:

/s/B. Lynne Parshall, attorney-in-fact 11/11/2015

** 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.