

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>BERTHELSEN SPENCER R</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>07/01/2013</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	07/02/2013	07/02/2013	M ⁽¹⁾		313 ⁽¹⁾	A	\$0	39,613	D	
Common Stock								70	I	By Daughter

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)	\$28.47	07/01/2013	07/01/2013	A		11,250		07/01/2014 ⁽²⁾	06/30/2023	Common Stock	11,250	\$0	11,250	D	
Restricted Stock Units	⁽³⁾	07/01/2013	07/01/2013	A		1,875		⁽⁴⁾	⁽⁴⁾	Common Stock	1,875	\$0	1,875	D	
Restricted Stock Units	⁽³⁾	07/02/2013	07/02/2013	M			313	⁽⁵⁾	⁽⁵⁾	Common Stock	313	\$0	937	D	

Explanation of Responses:

- Acquired pursuant to vesting and release of shares pursuant to a Restricted Stock Unit award granted on July 2, 2012.
- Grant of 7/1/13 to reporting person of stock options under the 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 7/1/14. The option shall be fully vested and exercisable on 7/1/17. The option is exercisable as to 0 shares on 7/1/13.
- Each restricted stock unit represents a contingent right to receive one share of Isis common stock, or its equivalent cash value.
- The restricted stock units vest in four equal annual installments, the first installment vesting on 7/1/14. Upon vesting, the restricted stock units will be paid out in whole shares of Isis common stock or cash as may be determined by the Company. The RSU shall be fully vested on 7/1/17. The RSU is vested as to 0 shares on 7/1/13.
- Restricted Stock Unit Award granted on 7/2/12. Restricted Stock Units vest in equal annual installments, the first installment vested on 7/2/13. Upon vesting, the restricted stock units will be paid out in whole shares of Isis Common Stock or cash as may be determined by the Company. The RSU will be fully vested on 7/2/16.

Remarks:

/s/B. Lynne Parshall, Attorney-in-Fact 07/03/2013

** 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.

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.