

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>05/21/2012</u>	
	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 Form filed by More than One Reporting Person

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	05/21/2012	05/21/2012	M ⁽¹⁾		2,731 ⁽¹⁾	A	\$9.4	32,031	D	
Common Stock	05/21/2012	05/21/2012	S ⁽¹⁾		2,731 ⁽¹⁾	D	\$9.42	29,300	D	
Common Stock	05/22/2012	05/22/2012	M ⁽¹⁾		17,269 ⁽¹⁾	A	\$9.4	46,569	D	
Common Stock	05/22/2012	05/22/2012	S ⁽¹⁾		17,269 ⁽¹⁾	D	\$9.56	29,300	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					
Director Stock Option (right to buy)	\$9.4	05/21/2012	05/21/2012	M			2,731	05/31/2006	05/30/2012	Common Stock 2,731	\$0	17,269	D	
Director Stock Option (right to buy)	\$9.4	05/22/2012	05/22/2012	M			17,269	05/31/2006	05/30/2012	Common Stock 17,269	\$0	0	D	

Explanation of Responses:

1. Acquired as a result of exercising a stock option that was scheduled to expire on 5/30/12. 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 3/1/12.

Remarks:

/s/B. Lynne Parshall

05/22/2012

** 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.