

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

OMB APPROVAL	
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Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934 or Section 30(h) of the Investment Company Act of 1940

<b>1. Name and Address of Reporting Person*</b> <b>BERTHELSEN SPENCER R</b>  (Last) (First) (Middle) <b>C/O ISIS PHARMACEUTICALS, INC.</b> <b>2855 GAZELLE COURT</b>  (Street) <b>CARLSBAD CA 92010</b>  (City) (State) (Zip)			<b>2. Issuer Name and Ticker or Trading Symbol</b> <b>ISIS PHARMACEUTICALS INC [ ISIS ]</b>			<b>5. Relationship of Reporting Person(s) to Issuer</b> (Check all applicable) <input checked="" type="checkbox"/> Director 10% Owner Officer (give title below) Other (specify below)		
			<b>3. Date of Earliest Transaction (Month/Day/Year)</b> <b>07/01/2015</b>					
			<b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>			<b>6. Individual or Joint/Group Filing (Check Applicable Line)</b> <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	07/01/2015	07/01/2015	M <sup>(1)</sup>		469	A	\$0	60,864	D	
Common Stock	07/01/2015	07/01/2015	M <sup>(2)</sup>		667	A	\$0	61,531	D	
Common Stock	07/02/2015	07/02/2015	M <sup>(3)</sup>		312	A	\$0	61,843	D	
Common Stock								70 <sup>(4)</sup>	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
Restricted Stock Units	(5)	07/01/2015	07/01/2015	M			469	(6)	(6)	Common Stock	469	\$0	937	D	
Restricted Stock Units	(5)	07/01/2015	07/01/2015	M			667	(7)	(7)	Common Stock	667	\$0	2,000	D	
Restricted Stock Units	(5)	07/02/2015	07/02/2015	M			312	(8)	(8)	Common Stock	312	\$0	312	D	
Restricted Stock Units	(5)	07/01/2015	07/01/2015	A			2,667	(9)	(9)	Common Stock	2,667	\$0	2,667	D	
Director Stock Option (right to buy)	\$57.16	07/01/2015	07/01/2015	A			16,000	07/01/2016 <sup>(10)</sup>	06/30/2025 <sup>(10)</sup>	Common Stock	16,000	\$0	16,000	D	

**Explanation of Responses:**

- Acquired pursuant to vesting and release of shares pursuant to a Restricted Stock Unit award granted on July 1, 2013.
- Acquired pursuant to vesting and release of shares pursuant to a Restricted Stock Unit award granted on July 1, 2014.
- Acquired pursuant to vesting and release of shares pursuant to a Restricted Stock Unit award granted on July 2, 2012.
- The reporting person disclaims beneficial ownership of all securities held by his daughter, and this report should not be deemed an admission that the reporting person is the beneficial owner of such securities for purposes of Section 16 or for any other purpose.
- Each Restricted Stock Unit represents a contingent right to receive one share of Isis common stock, or its equivalent cash value.
- Restricted Stock Unit Award granted on July 1, 2013. Restricted Stock Units vest in equal annual installments, the first installment vested on July 1, 2014. 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 July 1, 2017.
- Restricted Stock Unit Award granted on July 1, 2014. Restricted Stock Units vest in equal annual installments, the first installment vested on July 1, 2015. 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 July 1, 2018.
- Restricted Stock Unit Award granted on July 2, 2012. Restricted Stock Units vest in equal annual installments, the first installment vested on July 2, 2013. 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 July 2, 2016.
- Grant of July 1, 2015 to reporting person of Restricted Stock Unit Award under the Isis Pharmaceuticals, Inc. Amended and Restated 2002 Non-Employee Directors' Stock Option Plan. Restricted Stock Units vest in four equal annual installments, the first installment vesting on July 1, 2016. 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 July 1, 2019. The RSU is vested as to 0 shares on July 1, 2015.
- Grant of July 1, 2015 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 7/1/2016. The option shall be fully vested and exercisable on 7/1/2019. The stock option was exercisable as to 0 shares on 7/1/2015.

**Remarks:**

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

07/02/2015

\*\* 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.

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