FORM 4

UNITED STATES SECURITIES AND EXCHANGE COMMISSION

| Washington, D.C. 20549 |) |
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STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

| ı | OMB APPRO | JVAL | | | | | |
|---|--------------------------|-----------|--|--|--|--|--|
| | OMB Number: | 3235-0287 | | | | | |
| l | Estimated average burden | | | | | | |
| | hours per response: | 0.5 | | | | | |
| | | | | | | | |

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

| 1. Name and Address of Reporting Person* <u>ISIS PHARMACEUTICALS INC</u> | | | | | | 2. Issuer Name and Ticker or Trading Symbol Regulus Therapeutics Inc. [RGLS] | | | | | | | | 5. Relationship of Reporting Person(s) to Issuer (Check all applicable) X Director X 10% Owner | | | | |
|--|------|-------------------|---|-----------------|---|---|--|-------------------------|------------------|---|-----------------------|----------------------|--------------------------------------|--|---|--|-------------------------|------------------|
| (Last) 2855 GA | (Fir | , | Middle) | | | 3. Date of Earliest Transaction (Month/Day/Year) 09/10/2014 | | | | | | | | | Offic belov | er (give title v) | Othe belov | r (specify v) |
| (Street) CARLSBAD CA 92010 (City) (State) (Zip) | | | | | . If Amendment, Date of Original Filed (Month/Day/Year) | | | | | | | 6. Indiv Line) | Form filed by One Reporting Person | | | | | |
| | | Tabl | e I - N | on-Deriv | ative | Seci | uritie | s Ac | quire | d, Di | sposed o | f, or E | Benefic | cially | Owne | ed | | |
| 1. Title of Security (Instr. 3) 2. Transactic Date (Month/Day/ | | | | Execution Date, | | | 3. Transa Code (8) | | | 4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 a | | | Secur Benef Owne | icially d Following | 6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4) | 7. Nature of Indirect Beneficial Ownership | | |
| | | | | | | | | | Code | v | Amount | (A) or (D) | Price | | | ted action(s) 3 and 4) | | (Instr. 4) |
| Common Stock 09/10/2014 | | | | | 014 | | | | S ⁽¹⁾ | | 2,000 | D | \$7.6 | 996(2) | 6,9 | 964,600 | D ⁽³⁾ | |
| Common Stock 09/11/2014 | | | | |)14 | | | S ⁽¹⁾ | | 3,400 | D | \$7.8 | 341(4) | 41 ⁽⁴⁾ 6,961,200 | | D ⁽³⁾ | | |
| Common Stock 09/12/2014 | | | | | | | | S ⁽¹⁾ | | 3,500 | D | \$7.9 | 602(5) | 6,957,700 6,957,700 | | D ⁽³⁾ | | |
| | | Та | ble II | | | | | | | | osed of, convertib | | | | wned | | | |
| 1. Title of Derivative Security (Instr. 3) 2. Conversion or Exercise Price of Derivative Security Security 3. Transaction Date Executio if any (Month/Day/Year) | | ion Date, | 4. Transaction Code (Instr. 8) | | 5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5) | | 6. Date Exerc Expiration Da (Month/Day/Y | | ate | 7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4) | | Deri Sec (Inst | rice of vative urity tr. 5) | 9. Number of derivative Securities Beneficially Owned Following Reported Transaction((Instr. 4) | Ownership Form: Direct (D) or Indirect (I) (Instr. 4) | 11. Nature of Indirect Beneficial Ownership (Instr. 4) | | |
| | | | | | Code | v | (A) | (D) | Date Exerci | sable | Expiration Date | Title | Amoun or Numbe of Shares | | | | | |
| | | Reporting Person* | INC | | | | | | | | | | | | | | | |

| 1. Name and Address of Reporting Person* ISIS PHARMACEUTICALS INC | | | | | | | | | |
|--|---------------|----------|--|--|--|--|--|--|--|
| (Last) | Last) (First) | | | | | | | | |
| 2855 GAZELLE COURT | | | | | | | | | |
| (Street) | | | | | | | | | |
| CARLSBAD | CA | 92010 | | | | | | | |
| (City) | (State) | (Zip) | | | | | | | |
| 1. Name and Address of Reporting Person* PARSHALL B LYNNE | | | | | | | | | |
| (Last) (First) | | (Middle) | | | | | | | |
| C/O ISIS PHARMACEUTICALS, INC. | | | | | | | | | |
| 2855 GAZELLE COURT | | | | | | | | | |
| (Street) | | | | | | | | | |
| CARLSBAD | CA | 92010 | | | | | | | |
| (City) | (State) | (Zip) | | | | | | | |

Explanation of Responses:

- 1. The sales reported in the Form 4 were effected pursuant to a Rule 10b5-1 trading plan adopted by the reporting person on May 22, 2014.
- 2. The price reported in Column 4 is a weighted average price. These shares were sold in multiple transactions at prices ranging from \$7.45 to \$7.85 inclusive. The reporting person undertakes to provide to RGLS, any security holder of RGLS, 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 this footnote to this Form 4.
- 3. The shares are held directly by Isis Pharmaceuticals, Inc. Ms. Parshall is an officer and director of Isis and therefore may be deemed to have voting or investment power over the shares beneficially owned by

Isis. Ms. Parshall disclaims beneficial ownership over the shares beneficially owned by Isis, except to the extent of her proportionate pecuniary interest therein as a stockholder of Isis.

4. The price reported in Column 4 is a weighted average price. These shares were sold in multiple transactions at prices ranging from \$7.70 to \$8.02 inclusive. The reporting person undertakes to provide to RGLS, any security holder of RGLS, 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 this footnote to this Form 4.

5. The price reported in Column 4 is a weighted average price. These shares were sold in multiple transactions at prices ranging from \$7.83 to \$8.03 inclusive. The reporting person undertakes to provide to RGLS, any security holder of RGLS, 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 this footnote to this Form 4.

Remarks:

/s/ Christopher Aker, Attorneyin-Fact for All Reporting 09/12/2014
Persons
** 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.