## FORM 4

## UNITED STATES SECURITIES AND EXCHANGE COMMISSION

| Washington, | D.C. | 20549 |
|-------------|------|-------|
|-------------|------|-------|

STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

| OMB APPROVAL             |     |  |  |  |  |  |  |
|--------------------------|-----|--|--|--|--|--|--|
| OMB Number: 3235-0287    |     |  |  |  |  |  |  |
| 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

|  |  |                   |   |   | 01 .   | Section | 1 30(11)   | or trie                                    | IIIVESIII        | ieni C  | ompany Act                | JI 1940   |   |                                 |                                    |  |   |                  |  |
|--|--|-------------------|---|---|--|---------|--|--|------------------|---|---------------------------|---|---|---------------------------------|------------------------------------|--|---|------------------|--|
| 1. Name and Address of Reporting Person*  ISIS PHARMACEUTICALS INC |  |                   |   |   | 2. Issuer Name and Ticker or Trading Symbol Regulus Therapeutics Inc. [ "RGLS" ] |         |  |  |                  |   |                           |   | Relationship of Reporting Person(s) to Issuer (Check all applicable)     X Director X 10% Owner |                                 |                                    |  |   |                  |  |
|  |  |                   |   | 3. Date of Earliest Transaction (Month/Day/Year) 07/16/2014 |  |         |  |  |                  |   |                           |   | Offic<br>below  | er (give title<br>w)            |                                    | Other<br>below)                              | (specify  |                  |  |
| (Street)   | BAD CA   | A 9               | 92010   |   | - 4. If  | f Amen  | Amendment, Date of Original Filed (Month/Day/Year) |  |                  |   |                           |   |   | 6. Indiv<br>Line)               | Form filed by One Reporting Person |  |   |                  |  |
| (City)   | (St  | ate) (            | Zip)  |   |  |         |  |  |                  |   |                           |   |   |                                 |                                    |  |   |                  |  |
|  |  | Tabl              | le I - N  | on-Deriv  | ative  | Sec     | uritie   | s Ac                                       | quire            | d, Di   | sposed o                  | f, or B   | enefic  | cially                          | Owne                               | ed   |   |                  |  |
| 1. Title of Security (Instr. 3)                                    |  |                   | 2. Transaction<br>Date<br>(Month/Day/Year)  |   | Execution Date,<br>Year) if any  |         | Transaction Dispo                                  |  |                  | 4. Securities Acquired (A) or<br>Disposed Of (D) (Instr. 3, 4 a |                           |   | Secur<br>Benef<br>Owne  | ficially<br>d Following         | Form                               | nership<br>: Direct<br>r Indirect<br>str. 4) | 7. Nature<br>of Indirect<br>Beneficial<br>Ownership |                  |  |
|  |  |                   |   |   |  |         | Code   | v  | Amount           | (A) or<br>(D)   | Price                     |   |   | rted<br>action(s)<br>. 3 and 4) |                                    |  | (Instr. 4)  |                  |  |
| Common Stock (   |  |                   |   | 07/16/2   | 2014   |         |  |  | S <sup>(1)</sup> |   | 3,500                     | D   | \$6.5   | 881 <sup>(2)</sup>              | 7,0                                | 026,050                                      | 1   | D <sup>(3)</sup> |  |
| Common Stock 07/2  |  |                   |   | 07/17/2   | 2014   |         |  |  | S <sup>(1)</sup> |   | 5,000                     | D   | \$6.5   | 812(4)                          | 7,0                                | 021,050                                      | ]   | D <sup>(3)</sup> |  |
| Common Stock 07/18/20  |  |                   | 2014  | 014   |  |         | S <sup>(1)</sup>                                   |  | 5,000            | D   | \$6.8                     | \$6.8002(5)   |   | 7,016,050                       |                                    | D <sup>(3)</sup>                             |   |                  |  |
|  |  | Та                | able II   |   |  |         |  |  |                  |   | osed of,<br>convertib     |   |   |                                 | wned                               |  |   |                  |  |
| 1. Title of<br>Derivative<br>Security<br>(Instr. 3)                | Title of 2. 3. Transaction Bate Conversion Of Conversion of Code (Instr. Derivative curity or Exercise (Month/Day/Year) if any Code (Instr. Derivative |                   | 6. Date Exercisable and Expiration Date (Month/Day/Year)  7. Title and Amount of Securities Underlying Derivative Security (Instrant 4) |   |  |         | t of<br>ies<br>/ing<br>ive                         | 8. Price of Derivative Security (Instr. 5) |                  |   | O<br>Fe<br>D<br>oi<br>(I) | o.<br>wnership<br>orm:<br>irect (D)<br>r Indirect<br>) (Instr. 4) | Beneficial<br>Ownership<br>(Instr. 4)   |                                 |                                    |  |   |                  |  |
|  |  |                   |   |   | Code   | v       | (A)  | (D)  | Date<br>Exerci   | sable   | Expiration<br>Date        | Title   | Amoun<br>or<br>Number<br>of<br>Shares   |                                 |                                    |  |   |                  |  |
|  |  | Reporting Person* | INC   |   |  |         |  |  |                  |   |                           |   |   |                                 |                                    |  |   |                  |  |

| 1. Name and Address of Reporting Person*  ISIS PHARMACEUTICALS INC |         |          |  |  |  |  |  |  |  |  |
|--|---------|----------|--|--|--|--|--|--|--|--|
| (Last)   | (First) | (Middle) |  |  |  |  |  |  |  |  |
| 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 \$6.52 to \$6.74 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 \$6.48 to \$6.61 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 \$6.58 to \$6.95 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, By: for all Reporting
Owners

\*\* 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.