

Regulus Therapeutics Inc.  
Form POS AM  
April 29, 2016  
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As filed with the Securities and Exchange Commission on April 29, 2016

Registration No. 333-203292

**UNITED STATES**  
**SECURITIES AND EXCHANGE COMMISSION**  
**WASHINGTON, D.C. 20549**

**POST-EFFECTIVE AMENDMENT NO. 5**

**to**

**Form S-3**

**REGISTRATION STATEMENT**

***UNDER***

***THE SECURITIES ACT OF 1933***

**Regulus Therapeutics Inc.**

**(Exact name of registrant as specified in its charter)**

**Delaware** **26-4738379**  
**(State or other jurisdiction of** **(IRS Employer**  
**incorporation or organization)** **Identification Number)**  
**3545 John Hopkins Ct., Suite 210**  
**San Diego, CA 92121**

**(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)**

**Paul C. Grint, M.D.**  
**President and Chief Executive Officer**  
**Regulus Therapeutics Inc.**  
**3545 John Hopkins Ct., Suite 210**  
**San Diego, CA 92121**  
**(858) 202-6300**

**(Name, address, including zip code, and telephone number, including area code, of agent for service)**

*Copies to:*

**Thomas A. Coll, Esq.**  
**Kenneth J. Rollins, Esq.**  
**Cooley LLP**  
**4401 Eastgate Mall**  
**San Diego, CA 92121**  
**(858) 550-6000**

**Approximate date of commencement of proposed sale to public:** From time to time after the effective date of this Registration Statement.

If the only securities being registered on this form are being offered pursuant to dividend or interest reinvestment plans, please check the following box. "

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If any of the securities being registered on this form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box.

If this form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this form is a registration statement pursuant to General Instruction I.D. or a post-effective amendment thereto that shall become effective upon filing with the Commission pursuant to Rule 462(e) under the Securities Act, check the following box.

If this form is a post-effective amendment to a registration statement filed pursuant to General Instruction I.D. filed to register additional securities or additional classes of securities pursuant to Rule 413(b) under the Securities Act, check the following box.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

|  |   |
|--|---|
| Large accelerated filer <input type="checkbox"/>   | Accelerated filer <input checked="" type="checkbox"/> |
| Non-accelerated filer <input type="checkbox"/> (Do not check if a smaller reporting company) | Smaller reporting company <input type="checkbox"/>    |

**The registrant hereby amends this registration statement on such date or dates as may be necessary to delay its effective date until the registrant shall file a further amendment that specifically states that this registration statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act or until the registration statement shall become effective on such date as the Securities and Exchange Commission, acting pursuant to said Section 8(a), may determine.**

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**EXPLANATORY NOTE**

This Post-Effective Amendment No. 5 to the Registration Statement on Form S-3 (File No. 333-203292) is being filed solely for the purpose of filing Exhibit 23.1 to the Registration Statement and updating Item 16 of the Registration Statement and the Exhibit Index accordingly. This amendment is not intended to amend or delete any part of the Registration Statement except as specifically noted herein.

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**The information in this prospectus is not complete and may be changed. A registration statement relating to these securities has been declared effective by the Securities and Exchange Commission. This prospectus is not an offer to sell these securities and is not soliciting an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.**

**SUBJECT TO COMPLETION, DATED APRIL 29, 2016**

PROSPECTUS

**\$150,000,000**

**Common Stock**

597,833 Shares of Common Stock

Offered by Selling Stockholder

We may from time to time offer to sell up to \$150,000,000 of our common stock pursuant to this prospectus. In addition, the selling stockholder identified in this prospectus may sell, from time to time, up to 597,833 shares of our common stock. We will not receive any proceeds from sales by the selling stockholder.

This prospectus describes some of the general terms that may apply to an offering of our common stock. The specific terms and any other information relating to a specific offering will be set forth in a supplement to this prospectus to the extent required by applicable law. We may also authorize one or more free writing prospectuses to be provided to you in connection with these offerings. The prospectus supplement or free writing prospectus, as applicable, may also add, update or change information contained in this prospectus with respect to that specific offering. You should read this prospectus, the information incorporated by reference into this prospectus and any applicable prospectus supplement or free writing prospectus carefully before you invest.

Our common stock may be offered and sold in the same offering or in separate offerings, directly by us to investors, through agents designated from time to time or to or through underwriters or dealers, or through a combination of these methods. For additional information on the methods of sale, you should refer to the section entitled "Plan of Distribution" in this prospectus and in the applicable prospectus supplement. If any agents or underwriters are involved in the sale of any common stock with respect to which this prospectus is being delivered, the names of such agents or underwriters and any applicable fees, commissions, discounts and options to purchase additional shares will be set forth in a prospectus supplement. The price to the public of our common stock and the net proceeds we expect to receive from such sale will also be set forth in a prospectus supplement.



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**We have not authorized anyone to provide you with information other than the information contained in or incorporated by reference into this prospectus or any applicable prospectus supplement or free writing prospectus that we may authorize in connection with an offering of our common stock. We are not making an offer to sell or seeking an offer to buy shares of our common stock under this prospectus or any applicable prospectus supplement or free writing prospectus in any jurisdiction where the offer or sale is not permitted. The information contained in this prospectus, any applicable prospectus supplement or free writing prospectus, and the documents incorporated by reference herein and therein are accurate only as of their respective dates, regardless of the time of delivery of this prospectus or any sale of a security.**



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**ABOUT THIS PROSPECTUS**

This prospectus is part of a registration statement on Form S-3 that we filed with the Securities and Exchange Commission, or the SEC, using the shelf registration process. Under this shelf registration process, we may offer and sell from time to time in one or more offerings the common stock described in this prospectus up to a total dollar amount of \$150,000,000. In addition, under this shelf process, the selling stockholder may sell from time to time up to 597,833 shares of our common stock.

This prospectus provides you with a general description of our common stock that we and/or the selling stockholder may offer. Each time we and/or the selling stockholder offer shares of our common stock under this prospectus, we will provide a prospectus supplement that will contain more specific information about the terms of that offering. We may also authorize one or more free writing prospectuses to be provided to you that may contain material information relating to an offering of our common stock. We may also add, update or change in any prospectus supplement (and in any related free writing prospectus that we may authorize to be provided to you) any of the information contained in this prospectus or in the documents that we have incorporated by reference into this prospectus. We urge you to carefully read this prospectus, any applicable prospectus supplement and any related free writing prospectus, together with the information incorporated herein by reference as described under the headings *Where You Can Find More Information* and *Incorporation of Certain Information Reference* before buying any of the common stock being offered.

In this prospectus, unless otherwise stated or the context otherwise requires, the terms *Regulus*, *the Company*, *we*, *us* and *our* refer to Regulus Therapeutics Inc. Each of the trade names or service marks appearing or incorporated by reference in this prospectus or any applicable prospectus supplement are the property of their respective owners.

**This prospectus may not be used to consummate a sale of common stock unless, to the extent required by applicable law, it is accompanied by a prospectus supplement.**

You should rely only on the information contained in, or incorporated by reference into, this prospectus and any applicable prospectus supplement, along with the information contained in any free writing prospectuses we have authorized for use in connection with a specific offering. Neither we nor the selling stockholder have authorized anyone to provide you with different or additional information. You must not rely upon any information or representation not contained or incorporated by reference in this prospectus, any accompanying prospectus supplement or in any related free writing prospectus that we may authorize to be provided to you. This prospectus is an offer to sell only the common stock offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so.

The information appearing in this prospectus, any applicable prospectus supplement or any related free writing prospectus is accurate only as of the date on the front of the document and any information we have incorporated by reference is accurate only as of the date of the document incorporated by reference, regardless of the time of delivery of this prospectus, any applicable prospectus supplement or any related free writing prospectus, or any sale of a security. Our business, financial condition, results of operations and prospects may have changed since those dates.

This prospectus contains and incorporates by reference market data and industry statistics and forecasts that are based on independent industry publications and other publicly available information. Although we believe that these sources are reliable, we do not guarantee the accuracy or completeness of this information and we have not independently verified this information. Although we are not aware of any misstatements regarding the market and industry data presented in this prospectus and the documents incorporated herein by reference, these estimates involve risks and uncertainties and are subject to change based on various factors, including those discussed under the heading *Risk*

Factors contained in any applicable prospectus supplement and any related

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free writing prospectus, and under similar headings in the other documents that are incorporated by reference into this prospectus. Accordingly, investors should not place undue reliance on this information.

This prospectus contains summaries of certain provisions contained in some of the documents described herein, but reference is made to the actual documents for complete information. All of the summaries are qualified in their entirety by the actual documents. Copies of some of the documents referred to herein have been filed, will be filed or will be incorporated by reference as exhibits to the registration statement of which this prospectus is a part, and you may obtain copies of those documents as described below under the section entitled **Where You Can Find More Information**.

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**SUMMARY**

**The Company**

We are a biopharmaceutical company focused on discovering and developing first-in-class drugs that target *microRNAs* to treat a broad range of diseases. We were formed in 2007 when Alnylam Pharmaceuticals, Inc., or Alnylam, and Ionis Pharmaceuticals, Inc. (formerly Isis Pharmaceuticals, Inc.), or Ionis, contributed significant intellectual property, know-how and financial and human capital to pursue the development of drugs targeting *microRNAs* pursuant to a license and collaboration agreement. We have established strategic alliances with AstraZeneca AB and Sanofi to discover, develop and commercialize *microRNA* therapeutics. Under these strategic alliances, we are eligible to receive approximately \$900.0 million in aggregate milestone payments upon successful commercialization of *microRNA* therapeutics for the programs contemplated by our agreements. These payments include up to \$105.3 million upon achievement of preclinical and investigational new drug, or IND, milestones, up to \$128.0 million upon achievement of clinical development milestones, up to \$180.0 million upon achievement of regulatory milestones and up to \$490.0 million upon achievement of commercialization milestones.

*microRNAs* are naturally occurring ribonucleic acid, or RNA, molecules that play a critical role in regulating key biological pathways. Scientific research has shown that the improper balance, or dysregulation, of *microRNAs* is directly linked to many diseases. To date, approximately 500 *microRNAs* have been identified in humans, each of which is believed to interact with a specific set of genes that control key aspects of cell biology. Since most diseases are multi-factorial and involve multiple targets in a pathway, the ability to modulate gene networks by targeting a single *microRNA* provides a new therapeutic approach for treating complex diseases.

RNA plays an essential role in the process used by cells to encode and translate genetic information from DNA to proteins. RNA is comprised of subunits called nucleotides and is synthesized from a DNA template by a process known as transcription. Transcription generates different types of RNA, including messenger RNAs that carry the information for proteins in the sequence of their nucleotides. In contrast, *microRNAs* are RNAs that do not code for proteins but rather are responsible for regulating gene expression by affecting the translation of target messenger RNAs. By interacting with many messenger RNAs, a single *microRNA* can regulate several genes that are instrumental for the normal function of a biological pathway.

We believe that *microRNA* therapeutics have the potential to become a new and major class of drugs with broad therapeutic application for the following reasons:

*microRNAs*, until recently, have not been a focus of pharmaceutical research;

*microRNAs* play a critical role in regulating biological pathways by controlling the translation of many target genes;

*microRNA* therapeutics target entire disease pathways which may result in more effective treatment of complex multi-factorial diseases; and

*microRNA* therapeutics may be synergistic with other therapies because of their different mechanism of action.

We believe we have assembled the leading position in the *microRNA* field, including expertise in *microRNA* biology and oligonucleotide chemistry, a broad intellectual property estate, relationships with key opinion leaders and a disciplined drug discovery and development process. We refer to these assets as our *microRNA* product platform. We are using our *microRNA* product platform to develop chemically modified, single-stranded oligonucleotides that we call anti-miRs to modulate *microRNAs* and return diseased cells to their healthy state. We believe *microRNAs* may be transformative in the field of drug discovery and that anti-miRs may become a new and major class of drugs with broad therapeutic application, much like small molecules,

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biologics and monoclonal antibodies. In addition to our *microRNA* product platform, we have established Regulus *microMarkers*<sup>SM</sup>, a division focused on identifying *microRNAs* as biomarkers of human disease to support our therapeutic pipeline, collaborators and strategic partners. Regulus *microMarkers*<sup>SM</sup> utilizes a clinically-validated, highly reproducible technology platform to identify *microRNAs* as potential biomarkers for disease and we control key intellectual property and know-how related to the division. We believe that *microRNA* biomarkers may be used to select optimal patient segments in clinical trials and to monitor disease progression or relapse. We believe these *microRNA* biomarkers can be applied toward drugs that we develop and drugs developed by other companies with which we partner or collaborate. We have completed a research collaboration with Biogen Idec focused on the discovery of *microRNAs* as biomarkers for multiple sclerosis and have also completed research for another leading, commercial-stage pharmaceutical company to explore *microRNAs* as biomarkers for specific patient populations. We also maintain several academic research collaborations focused on the identification of *microRNAs* as biomarkers in multiple disease areas.

## **Corporate Information**

We were originally formed as a limited liability company under the name Regulus Therapeutics LLC in the State of Delaware in September 2007. In January 2009, we converted Regulus Therapeutics LLC to a Delaware corporation and changed our name to Regulus Therapeutics Inc. Our principal executive offices are located at 3545 John Hopkins Court, Suite 210, San Diego, California 92121, and our telephone number is (858) 202-6300. Our corporate website address is [www.regulusrx.com](http://www.regulusrx.com). Information contained on or accessible through our website is not a part of this prospectus, and the inclusion of our website address in this prospectus is an inactive textual reference only.

We use Regulus Therapeutics as a trademark in the United States and other countries. We have filed for registration of this trademark in the United States and have registered it in the United States, the European Union and Switzerland. We use *microMarkers* as a servicemark in the United States and other countries. We have filed for registration of this servicemark in the United States. This prospectus contains references to our trademarks and to trademarks belonging to other entities. Solely for convenience, trademarks and trade names referred to in this prospectus, including logos, artwork and other visual displays, may appear without the ® or symbols, but such references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights or the rights of the applicable licensor to these trademarks and trade names. We do not intend our use or display of other companies trade names or trademarks to imply a relationship with, or endorsement or sponsorship of us by, any other companies.

We are an emerging growth company, as defined in the Jumpstart Our Business Startups Act of 2012. We will remain an emerging growth company until the earlier of (a) December 31, 2017, (b) the last day of the fiscal year in which we have total annual gross revenue of at least \$1.0 billion, or (c) the last day of the fiscal year in which we are deemed to be a large accelerated filer, which means the market value of our common stock that is held by non-affiliates exceeds \$700.0 million as of the prior June 30th and (d) the date on which we have issued more than \$1.0 billion in non-convertible debt during the prior three-year period. We refer to the Jumpstart Our Business Startups Act of 2012 herein as the JOBS Act, and references herein to emerging growth company shall have the meaning associated with it in the JOBS Act.

## **The Securities That May Be Offered**

We may offer shares of our common stock from time to time in one or more offerings under this prospectus up to a dollar amount of \$150,000,000. In addition, the selling stockholder may offer up to 597,833 shares of common stock in one or more offerings and in any combination. A prospectus supplement, which we will provide in connection with each offering, will describe the specific amounts, prices and terms of the offering. This prospectus may not be used to consummate a sale of our common stock unless it is accompanied by a prospectus supplement.



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Throughout this prospectus, when we refer to the shares of our common stock being registered on behalf of the selling stockholder, we are referring to the shares of common stock that have been issued pursuant to the transactions described below. When we refer to the selling stockholder in this prospectus, we are referring to the investor in the private placements who is named in this prospectus as the selling stockholder and, as applicable, any donees, pledgees, transferees or other successors-in-interest selling shares received after the date of this prospectus from the selling stockholder as a gift, pledge, or other non-sale related transfer.

**Private Placements**

In January 2009, in connection with the conversion of Regulus Therapeutics LLC, a Delaware limited liability company, into Regulus Therapeutics Inc., we issued an aggregate of 7,599,000 shares of series A convertible preferred stock to Ionis in exchange for the membership interests held by Ionis in Regulus Therapeutics LLC immediately prior to such conversion. In March 2009, in connection with our series A convertible preferred stock financing, we issued and sold an aggregate of 5,000,000 shares of series A convertible preferred stock to Ionis at a purchase price of \$2.00 per share, for aggregate gross proceeds of \$10.0 million. In connection with the foregoing transactions, we entered into a Founding Investor Rights Agreement with Ionis pursuant to which we granted certain registration rights to Ionis. Upon completion of our initial public offering, the foregoing shares were converted into an aggregate of 6,299,500 shares of our common stock.

The issuances described above were exempt from registration under the Securities Act of 1933, as amended, or the Securities Act, pursuant to the exemption for transactions by an issuer not involving any public offering under Section 4(a)(2) of, and Regulation D promulgated under, the Securities Act.



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**RISK FACTORS**

*Investing in our common stock involves significant risks. Before making an investment decision, you should carefully consider the risks and other information we include or incorporate by reference in this prospectus and any prospectus supplement. In particular, you should consider the risk factors under the heading Risk Factors included in our most recent Annual Report on Form 10-K, which is on file with the SEC and is incorporated herein by reference, and which may be amended, supplemented or superseded from time to time by other reports we file with the SEC in the future. The risks and uncertainties we have described are not the only ones facing our company. Additional risks and uncertainties not currently known to us or that we currently deem immaterial may also affect our business operations. Additional risk factors may be included in a prospectus supplement relating to a particular offering of our common stock.*

**SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS**

This prospectus, any prospectus supplement and the documents incorporated by reference herein contain forward-looking statements within the meaning of Section 27A of the Securities Act and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, that involve substantial risks and uncertainties. All statements, other than statements of historical fact, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words anticipate, believe, continue, should, estimate, expect, intend, ma project, will, and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Such statements may include, but are not limited to, statements concerning the following:

the initiation, cost, timing, progress and results of, and our expected ability to undertake certain activities and accomplish certain goals with respect to, our research and development activities, preclinical studies and clinical trials;

our ability to obtain and maintain regulatory approval of our product candidates, and any related restrictions, limitations, and/or warnings in the label of an approved product candidate;

our ability to obtain funding for our operations;

our plans to research, develop and commercialize our product candidates;

our strategic alliance partners' election to pursue development and commercialization;

our ability to attract collaborators with development, regulatory and commercialization expertise;

future activities to be undertaken by our strategic alliance partners, collaborators and other third parties;

our ability to obtain and maintain intellectual property protection for our product candidates;

the size and growth potential of the markets for our product candidates, and our ability to serve those markets;

our ability to successfully commercialize, and our expectations regarding future therapeutic and commercial potential with respect to, our product candidates;

the rate and degree of market acceptance of our product candidates;

our ability to develop sales and marketing capabilities, whether alone or with potential future collaborators;

regulatory developments in the United States and foreign countries;

the performance of our third-party suppliers and manufacturers;

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the success of competing therapies that are or may become available;

the loss of key scientific or management personnel;

our ability to successfully secure and deploy capital;

our use of proceeds of any offering pursuant to this prospectus;

our expectations regarding the time during which we will be an emerging growth company under the JOBS Act; and

the accuracy of our estimates regarding expenses, future revenues, capital requirements and need for additional financing.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included and incorporated by reference in this prospectus that we believe could cause actual results or events to differ materially from the forward-looking statements that we make. See the section entitled "Risk Factors" herein for more information. You should consider these factors and other cautionary statements made in this prospectus and in the documents we incorporate by reference as being applicable to all related forward-looking statements wherever they appear in the prospectus and in the documents incorporated by reference. Unless specifically indicated, our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make. We do not assume any obligation to update any forward-looking statements.

**USE OF PROCEEDS**

Unless otherwise provided in any applicable prospectus supplement, we currently intend to use the net proceeds from the sale of our common stock offered by under this prospectus for general corporate purposes, including preclinical and clinical development of our *microRNA* development candidates, including accelerating the investment in the development of our lead candidate RG-101, and the identification and validation of additional *microRNA* targets, for our Regulus *microMarkers*<sup>SM</sup> division and for capital expenditures, working capital and other general corporate purposes. We may also use a portion of the net proceeds to in-license, acquire or invest in complementary *microRNA* businesses, technologies, products or assets. However, we have no current commitments or obligations to do so. We may set forth additional information on the use of proceeds from the sale of our common stock we offer under this prospectus in a prospectus supplement relating to the specific offering. We cannot currently allocate specific percentages of the net proceeds that we may use for the purposes specified above. As a result, our management will have broad discretion in the allocation of the net proceeds. Pending their use, we plan to invest the net proceeds from this offering in short- and intermediate-term, interest-bearing obligations, investment-grade instruments, certificates of deposit or direct or guaranteed obligations of the U.S. government.

We will not receive any proceeds from the sale of shares of our common stock by the selling stockholder.

**DESCRIPTION OF CAPITAL STOCK**

The following description of our common stock, together with any additional information we include in any applicable prospectus supplements, summarizes the material terms and provisions of our common stock that we and/or the selling stockholder may offer under this prospectus. For the complete terms of our common stock, please refer to our certificate of incorporation and bylaws, which are exhibits to the registration statement that includes this prospectus. The terms of our common stock may also be affected by Delaware law.

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### **Authorized Capital Stock**

Our certificate of incorporation currently authorizes us to issue up to 200,000,000 shares of common stock, \$0.001 par value, and 10,000,000 shares of preferred stock, \$0.001 par value.

As of January 31, 2016, we had 52,695,533 shares of common stock outstanding and no shares of preferred stock outstanding. We will describe the specific terms of any common stock we and/or the selling stockholder may offer in more detail in a prospectus supplement relating to the offering of shares of common stock.

### **Common Stock**

*Voting.* Our common stock is entitled to one vote for each share held of record on all matters submitted to a vote of the stockholders, including the election of directors, and does not have cumulative voting rights. Accordingly, the holders of a majority of the shares of our common stock entitled to vote in any election of directors can elect all of the directors standing for election.

*Dividends.* Subject to preferences that may be applicable to any then outstanding preferred stock, the holders of common stock are entitled to receive dividends, if any, as may be declared from time to time by our board of directors out of legally available funds.

*Liquidation.* In the event of our liquidation, dissolution or winding up, holders of our common stock will be entitled to share ratably in the net assets legally available for distribution to stockholders after the payment of all of our debts and other liabilities, subject to the satisfaction of any liquidation preference granted to the holders of any outstanding shares of preferred stock.

*Rights and Preferences.* Holders of our common stock have no preemptive, conversion or subscription rights, and there are no redemption or sinking fund provisions applicable to our common stock. The rights, preferences and privileges of the holders of our common stock are subject to, and may be adversely affected by, the rights of the holders of shares of any series of our preferred stock that we may designate and issue in the future.

*Fully Paid and Nonassessable.* All of our outstanding shares of common stock are, and any shares of common stock to be issued by us in an offering under this prospectus will be, fully paid and nonassessable.

### **Preferred Stock**

Our board of directors has the authority, without further action by the stockholders, to issue up to 10,000,000 shares of preferred stock in one or more series, to establish from time to time the number of shares to be included in each such series, to fix the rights, preferences and privileges of the shares of each wholly unissued series and any qualifications, limitations or restrictions thereon and to increase or decrease the number of shares of any such series, but not below the number of shares of such series then outstanding.

Our board of directors may authorize the issuance of preferred stock with voting or conversion rights that could adversely affect the voting power or other rights of the holders of the common stock. The issuance of preferred stock, while providing flexibility in connection with possible acquisitions and other corporate purposes, could, among other things, have the effect of delaying, deferring or preventing a change in our control that may otherwise benefit holders of our common stock and may adversely affect the market price of the common stock and the voting and other rights of the holders of common stock. As of the date of this prospectus, there are no shares of preferred stock outstanding and we have no current plans to issue any shares of preferred stock.

**Registration Rights**

The holders of 1,303,780 shares of common stock, or their transferees, have the right to require us to register their shares with the SEC following the date of this prospectus so that those shares may be publicly resold, or to include their shares in any registration statement we file on Form S-1 or Form S-3.

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*Form S-3 Registration Rights.* If we are eligible to file a registration statement on Form S-3, one or more holders of registration rights have the right to demand that we file a registration statement on Form S-3 so long as the aggregate value of the securities to be sold under the registration statement on Form S-3 is at least a specified dollar amount, subject to specified exceptions.

*Piggyback Registration Rights.* If we register any securities for public sale, holders of registration rights will have the right to include their shares in the registration statement. The underwriters of any underwritten offering will have the right to limit the number of shares having registration rights to be included in the registration statement, subject to specified limitations. We have complied with, or obtained waivers with respect to, any and all rights to have shares registered under this registration statement.

*Expenses of Registration.* Generally, we are required to bear all registration and selling expenses incurred in connection with the piggyback and Form S-3 registrations described above, other than underwriting discounts and commissions.

*Expiration of Registration Rights.* The piggyback and Form S-3 registration rights discussed above will terminate in February 2018 or at such earlier time as such shares are sold in a public offering pursuant to a registration statement or pursuant to Rule 144 of the Securities Act.

## **Anti-takeover Effects of Provisions of our Certificate of Incorporation, our Bylaws and Delaware Law**

We are subject to Section 203 of the Delaware General Corporation Law, or Section 203. Section 203 generally prohibits a public Delaware corporation from engaging in a business combination with an interested stockholder for a period of three years after the date of the transaction in which the person became an interested stockholder, unless:

prior to the date of the transaction, the board of directors of the corporation approved either the business combination or the transaction which resulted in the stockholder becoming an interested stockholder;

the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the number of shares outstanding (a) shares owned by persons who are directors and also officers and (b) shares owned by employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or

on or subsequent to the date of the transaction, the business combination is approved by the board and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least 66  $\frac{2}{3}$ % of the outstanding voting stock which is not owned by the interested stockholder.

Section 203 defines a business combination to include:

any merger or consolidation involving the corporation and the interested stockholder;

any sale, transfer, pledge or other disposition involving the interested stockholder of 10% or more of the assets of the corporation;

subject to exceptions, any transaction involving the corporation that has the effect of increasing the proportionate share of the stock of any class or series of the corporation beneficially owned by the interested stockholder;

subject to exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder; and

the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits provided by or through the corporation.



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In general, Section 203 defines an interested stockholder as any entity or person beneficially owning 15% or more of the outstanding voting stock of the corporation and any entity or person affiliated with or controlling or controlled by the entity or person.

## **Certificate of Incorporation and Bylaws**

Provisions of our certificate of incorporation and bylaws may delay or discourage transactions involving an actual or potential change in our control or change in our management, including transactions in which stockholders might otherwise receive a premium for their shares or transactions that our stockholders might otherwise deem to be in their best interests. Therefore, these provisions could adversely affect the price of our common stock. Among other things, our certificate of incorporation and bylaws:

permit our board of directors to issue up to 10,000,000 shares of preferred stock, with any rights, preferences and privileges as they may designate (including the right to approve an acquisition or other change in our control);

provide that the authorized number of directors may be changed only by resolution of the board of directors;

provide that all vacancies, including newly created directorships, may, except as otherwise required by law, be filled by the affirmative vote of a majority of directors then in office, even if less than a quorum;

require that any action to be taken by our stockholders must be effected at a duly called annual or special meeting of stockholders and not be taken by written consent;

provide that stockholders seeking to present proposals before a meeting of stockholders or to nominate candidates for election as directors at a meeting of stockholders must provide notice in writing in a timely manner and also specify requirements as to the form and content of a stockholder's notice;

do not provide for cumulative voting rights (therefore allowing the holders of a majority of the shares of common stock entitled to vote in any election of directors to elect all of the directors standing for election, if they should so choose); and

provide that special meetings of our stockholders may be called only by the Chairman of the Board, our Chief Executive Officer or by the board of directors pursuant to a resolution adopted by a majority of the total number of authorized directors.

The amendment of any of these provisions, with the exception of the ability of our board of directors to issue shares of preferred stock and designate any rights, preferences and privileges thereto, would require approval by the holders of at least 66  $\frac{2}{3}$ % of our then outstanding common stock.

## **NASDAQ Global Market Listing**

Our common stock is listed on The NASDAQ Global Market under the RGLS symbol.

**Transfer Agent and Registrar**

The transfer agent and registrar for our common stock is Computershare Trust Company, N.A. The transfer agent and registrar's address is 250 Royall Street, Canton, MA, 02021.

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**SELLING STOCKHOLDER**

This prospectus relates to the resale by the selling stockholder named herein of up to 597,833 shares of our common stock. For more information, see [Summary Private Placements](#) above.

In September 2007, we entered into a license and collaboration agreement with Alnylam and Ionis, which we subsequently amended, restated and superseded in January 2009, and further amended in June 2010, October 2011 and August 2013. Under the agreement, we acquired an exclusive, royalty-bearing, worldwide license, with rights to sublicense, to patent rights owned or licensed by Alnylam and Ionis to develop, manufacture and commercialize products covered by the licensed patent rights for use in *microRNA* compounds which are *microRNA* antagonists and *microRNA* therapeutics containing these compounds. In addition, we have certain rights to miR-mimics. Under the agreement, we granted to both Alnylam and Ionis a license to practice our intellectual property developed by us to the extent that it is useful specifically to Alnylam's RNAi programs or Ionis' single-stranded oligonucleotide programs, but not including *microRNA* compounds or therapeutics that are the subject of our exclusive licenses from Alnylam and Ionis.

We are required to use commercially reasonable efforts to develop and commercialize licensed products under the agreement. We are required to notify Alnylam and Ionis when a program reaches development stage (defined as initiation of good laboratory practices, or GLP, toxicology studies) and whether or not we intend to pursue the program. Under the agreement, both Alnylam and Ionis have an option to assume the development and commercialization of product candidates in a program that we do not pursue. If neither Alnylam nor Ionis exercises this option, we are required to use our best efforts to finalize a term sheet with a third party with respect to such program. In the event we are unable to complete a transaction with a third party, both Alnylam and Ionis have a second opt-in option.

If an election is made by either Alnylam or Ionis (but not both) to opt-in, such party will pay us a one-time fixed payment, the amount of which will depend on whether the first or the second opt-in option was exercised, with a higher amount due if the first opt-in option was exercised. Clinical and regulatory milestones are also payable to us in the event the opt-in election is exercised. Such milestones total \$64.0 million in the aggregate if the election is made during the first opt-in period or \$15.7 million in the aggregate if the election is made at the second opt-in period. Tiered royalties are payable to us as a percentage of net sales on all products commercialized by the opt-in party. These royalties range from the low to middle single digits depending upon the volume of sales. The opt-in party is also entitled to sublicense the development program to a third party. In such a case, we are also entitled to receive a percentage of the sublicense income received by the opt-in party. The percentage payable depends upon the point at which the opt-in party sublicenses the program and ranges from the low end of the 10 to 20% range to the high end of the 40 to 50% range. The opt-in party is only required to pay the higher of the clinical and regulatory milestones or the sublicense income received in any calendar quarter. The opt-in party is also responsible for all third party payments due under other agreements as a result of the development. In the event both Alnylam and Ionis elect to opt-in during either opt-in period, the parties have agreed to work together to amend the development plan to continue development of the project, including funding of such project and assignment of roles and responsibilities.

In the event we or one of our strategic alliance partners continues with the development of a program, each of Alnylam and Ionis are entitled to royalties as a percentage of net sales. For products that we independently commercialize, these royalties will be in the low single digits. For products commercialized by a third-party collaborator, the royalties will be either the same percentage of net sales as described above or, if the sublicense does not provide a specified level of royalties to us or upon our election, a percentage of the sublicense income received by us from the strategic alliance partner and a modified royalty. The modified royalty would be based upon the lower of the single digit percentage discussed above or one third of the royalty received by us after payments made by us to

third parties for development, manufacture and commercialization activities under other agreements. In addition, if we sublicense rights to a collaborator, we will be required to pay to each of Alnylam

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and Ionis a percentage of our sublicense income in the mid-single digits. We are also responsible for payments due to third parties under other agreements as a result of our development activities, including payments owed by Alnylam and/or Ionis under their agreements.

Under the October 2011 amendment, Alnylam and Ionis granted us the right to research *microRNA* mimics under the licensed intellectual property of Alnylam and Ionis. In the event we develop a miR-mimic, we must first obtain approval from Alnylam and/or Ionis, as applicable, and such approval is subject to the consent of applicable third parties, if any. No additional consideration will be owed by us to Alnylam or Ionis for granting approval. We have the right to sublicense our research rights. We granted to both Alnylam and Ionis a fully paid up, worldwide and exclusive license to any intellectual property developed by us and useful to their research programs and which are not *microRNA* antagonists or approved miR-mimics.

In August 2013, we entered into an amendment to the agreement, pursuant to which the parties agreed to our use of certain Alnylam-controlled intellectual property concerning the use and manufacture of GalNAc conjugates ( GalNAc Process Technology ) on a non-exclusive basis. We will generally not be permitted to sublicense or otherwise transfer the GalNAc Process Technology and other Alnylam licensed intellectual property rights relating to GalNAc conjugate technology without the prior written consent of Alnylam, subject to certain limited exceptions for sublicenses to third party collaboration partners. There were no financial terms related to this amendment.

The agreement expires on the earlier of the cessation of development of the potential royalty-bearing products prior to the commercial sale of any such products anywhere in the world or following the first commercial sale of such products, the expiration of royalty obligations determined on a country-by-country and product-by-product basis.

This table below was prepared based on information supplied to us by the selling stockholder and reflects holdings as of January 31, 2016. As used in this prospectus, the term *selling stockholder* includes the selling stockholder listed below, and any donees, pledges, transferees or other successors in interest selling shares received after the date of this prospectus from the selling stockholder as a gift, pledge, or other non-sale related transfer. The number of shares in the column *Number of Shares Being Offered* represents the shares that the selling stockholder may offer under this prospectus. The selling stockholder may sell some, all or none of its shares. The selling stockholder may, at any time and from time to time, offer and sell pursuant to this prospectus any or all of the shares set forth below in any type of transaction, as more fully described in the section entitled *Plan of Distribution* on page 13. We do not know how long the selling stockholder will hold the shares before selling them, and we currently have no agreements, arrangements or understandings with the selling stockholder regarding the sale of any of the shares.

The percentage ownership information after the offering is based on 52,695,533 shares of our common stock outstanding as of January 31, 2016. Unless otherwise indicated, beneficial ownership is determined in accordance with Section 13(d) of the Exchange Act and the rules and regulations thereunder, and is based upon information provided by each respective selling stockholder identified below.

| Name and Address                                  | Shares of                                       | Number of Shares | Shares of  |            |
|---|---|------------------|--|------------|
|   | Common Stock Beneficially Owned Before Offering |                  | Common Stock Beneficially Owned Following the Offering |            |
|   |   | Being Offered    | Number   | % of Class |
| Ionis Pharmaceuticals, Inc.<br>2855 Gazelle Court | 2,843,172                                       | 597,833          | 2,245,339  | 4.26%      |



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**PLAN OF DISTRIBUTION**

We or the selling stockholder may sell the common stock from time to time pursuant to underwritten public offerings, direct sales to the public, negotiated transactions, block trades or a combination of these methods. We or the selling stockholder may sell the common stock to or through underwriters or dealers, through agents, or directly to one or more purchasers. We may distribute the common stock from time to time in one or more transactions:

from time to time in one or more transactions at a fixed price or prices, which may be changed from time to time;

at market prices prevailing at the time of sale;

at prices related to such prevailing market prices; or

at negotiated prices.

We may also sell equity securities covered by this registration statement in an at the market offering as defined in Rule 415 under the Securities Act. Such offering may be made into an existing trading market for such securities in transactions at other than a fixed price, either:

on or through the facilities of The Nasdaq Global Market or any other securities exchange or quotation or trading service on which such securities may be listed, quoted or traded at the time of sale; and/or

to or through a market maker otherwise than on The Nasdaq Global Market or such other securities exchanges or quotation or trading services.

Such at-the-market offerings, if any, may be conducted by financial institutions acting as principal or agent.

Any applicable prospectus supplement or supplements (and any related free writing prospectus that we may authorize to be provided to you) will describe the terms of the offering of the common stock, including, to the extent applicable:

the name or names of the underwriters, if any;

the purchase price of the common stock or other consideration therefor, and the proceeds, if any, we will receive from the sale;

any over-allotment options under which underwriters may purchase additional common stock from us;

any agency fees or underwriting discounts and other items constituting agents' or underwriters' compensation;

any public offering price;

any discounts or concessions allowed or reallocated or paid to dealers; and

any securities exchange or market on which the common stock may be listed.

Only underwriters named in an applicable prospectus supplement will be underwriters of the common stock offered by such prospectus supplement.

If underwriters are used in the sale, they will acquire the common stock for their own account and may resell the common stock from time to time in one or more transactions at a fixed public offering price or at varying prices determined at the time of sale. The obligations of the underwriters to purchase the common stock will be subject to the conditions set forth in the applicable underwriting agreement. We or the selling stockholder may offer the common stock to the public through underwriting syndicates represented by managing underwriters or by underwriters without a syndicate. Subject to certain conditions, the underwriters will be obligated to purchase all of the common stock offered by an applicable prospectus supplement, other than common stock covered by any over-allotment option. Any public offering price and any discounts or concessions



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allowed or reallocated or paid to dealers may change from time to time. We or the selling stockholder may use underwriters with whom we have a material relationship. We will describe in any applicable prospectus supplement, naming the underwriter, the nature of any such relationship.

We or the selling stockholder may sell common stock directly or through agents we designate from time to time. We will name any agent involved in the offering and sale of common stock and we will describe any commissions we or the selling stockholder will pay the agent in an applicable prospectus supplement. Unless any applicable prospectus supplement states otherwise, our or the selling stockholder's agent will act on a best-efforts basis for the period of its appointment.

We or the selling stockholder may authorize agents or underwriters to solicit offers by certain types of institutional investors to purchase common stock from us or the selling stockholder at the public offering price set forth in an applicable prospectus supplement pursuant to delayed delivery contracts providing for payment and delivery on a specified date in the future. We will describe the conditions to these contracts and the commissions we or the selling stockholder must pay for solicitation of these contracts in an applicable prospectus supplement.

We or the selling stockholder may provide agents and underwriters with indemnification against civil liabilities, including liabilities under the Securities Act, or contribution with respect to payments that the agents or underwriters may make with respect to these liabilities. Agents and underwriters may engage in transactions with, or perform services for, us or the selling stockholder in the ordinary course of business.

Any underwriter may engage in over-allotment, stabilizing transactions, short-covering transactions and penalty bids in accordance with Regulation M under the Exchange Act. Over-allotment involves sales in excess of the offering size, which create a short position. Stabilizing transactions permit bids to purchase the underlying common stock so long as the stabilizing bids do not exceed a specified maximum price. Syndicate-covering or other short-covering transactions involve purchases of the common stock, either through exercise of the over-allotment option or in the open market after the distribution is completed, to cover short positions. Penalty bids permit the underwriters to reclaim a selling concession from a dealer when the common stock originally sold by the dealer are purchased in a stabilizing or covering transaction to cover short positions. Those activities may cause the price of the common stock to be higher than it would otherwise be. If commenced, the underwriters may discontinue any of the activities at any time.

Any underwriters or agents who are qualified market makers on the Nasdaq Global Select Market may engage in passive market making transactions in our common stock on the Nasdaq Global Select Market in accordance with Rule 103 of Regulation M, during the business day prior to the pricing of the offering, before the commencement of offers or sales of the common stock. Passive market makers must comply with applicable volume and price limitations and must be identified as passive market makers. In general, a passive market maker must display its bid at a price not in excess of the highest independent bid for such common stock; if all independent bids are lowered below the passive market maker's bid, however, the passive market maker's bid must then be lowered when certain purchase limits are exceeded. Passive market making may stabilize the market price of the common stock at a level above that which might otherwise prevail in the open market and, if commenced, may be discontinued at any time.

In compliance with guidelines of the Financial Industry Regulatory Authority, or FINRA, the maximum consideration or discount to be received by any FINRA member or independent broker dealer may not exceed 8% of the aggregate amount of the common stock offered pursuant to this prospectus and any applicable prospectus supplement.



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**LEGAL MATTERS**

The validity of the securities offered hereby is being passed upon for us by Cooley LLP, San Diego, California.

**EXPERTS**

Ernst & Young LLP, independent registered public accounting firm, has audited our financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2015, as set forth in their report, which is incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

**WHERE YOU CAN FIND MORE INFORMATION**

We file reports, proxy statements and other documents with the SEC as required by the Exchange Act. You can find, copy and inspect information we file at the SEC's public reference room at 100 F Street, N.E., Washington, D.C. 20549. You can call the SEC at 1-800-SEC-0330 for further information about the public reference room. You can review our electronically filed reports, proxy and information statements on the SEC's web site at [www.sec.gov](http://www.sec.gov) or on our web site at [www.regulusrx.com](http://www.regulusrx.com). Information included on our web site is not part of this prospectus or any prospectus supplement.

This prospectus is part of a registration statement that we filed with the SEC. The registration statement contains more information than this prospectus regarding us and our common stock, including exhibits and schedules. You can obtain a copy of the registration statement from the SEC at any address listed above or from the SEC's web site.

**INCORPORATION OF CERTAIN INFORMATION BY REFERENCE**

The SEC allows us to incorporate into this prospectus information that we file with the SEC in other documents. This means that we can disclose important information to you by referring to other documents that contain that information. Any information that we incorporate by reference is considered part of this prospectus.

Information contained in this prospectus and information that we file with the SEC in the future and incorporate by reference in this prospectus automatically modifies and supersedes previously filed information including information in previously filed documents or reports that have been incorporated by reference in this prospectus, to the extent the new information differs from or is inconsistent with the old information. Any information so modified or superseded shall not be deemed, except as so modified or superseded, to constitute a part of this prospectus.

We incorporate by reference, as of their respective dates of filing, the documents listed below that we have filed with the SEC and any documents that we file with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of this prospectus and prior to the termination of the last offering of common stock under this prospectus (except in each case the information contained in such documents to the extent furnished and not filed ):

our Annual Report on Form 10-K for the year ended December 31, 2015, filed with the SEC on February 23, 2016;

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the information specifically incorporated by reference into our Annual Report on Form 10-K for the year ended December 31, 2015 from our definitive proxy statement on Schedule 14A filed with the SEC on April 22, 2016;

our Current Reports on Form 8-K filed with the SEC on January 8, 2016 and February 17, 2016; and

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the description of our common stock contained in our registration statement on Form 8-A filed with the SEC on September 27, 2012, including any amendment or report filed for the purpose of updating such description.

You may also request a copy of these filings, at no cost, by writing us at 3545 John Hopkins Court, Suite 210, San Diego, California 92121 or telephoning us at (858) 202-6300.

Table of Contents**PART II****INFORMATION NOT REQUIRED IN PROSPECTUS****Item 14. Other Expenses of Issuance and Distribution.**

The following table sets forth the various expenses incurred or to be incurred in connection with the registration of the common stock being registered hereby, all of which will be borne by the Registrant. All amounts shown are estimates except the SEC registration fee.

|                              |                   |
|------------------------------|-------------------|
| SEC registration fee         | \$ 15,476         |
| Legal fees and expenses      | 300,000           |
| Accounting fees and expenses | 150,000           |
| Miscellaneous expenses       | 9,524             |
| <b>Total expenses</b>        | <b>\$ 475,000</b> |

**Item 15. Indemnification of Directors and Officers.**

The Registrant's certificate of incorporation and bylaws provide that each person who was or is made a party or is threatened to be made a party to or is otherwise involved in any action, suit or proceeding, whether civil, criminal, administrative or investigative, by reason of the fact that he or she is or was one of the Registrant's directors or officers or is or was serving at the Registrant's request as a director, officer, or trustee of another corporation, or of a partnership, joint venture, trust or other enterprise, whether the basis of such proceeding is alleged action in an official capacity as a director, officer or trustee or in any other capacity while serving as a director, officer or trustee, shall be indemnified and held harmless by the Registrant to the fullest extent authorized by the DGCL against all expense, liability and loss (including attorneys' fees) actually and reasonably incurred by such person in connection with the defense or settlement of such action.

Section 145 of the DGCL permits a corporation to indemnify any director or officer of the corporation against expenses (including attorneys' fees), judgments, fines and amounts paid in settlement actually and reasonably incurred in connection with any action, suit or proceeding brought by reason of the fact that such person is or was a director or officer of the corporation, if such person acted in good faith and in a manner that he or she reasonably believed to be in, or not opposed to, the best interests of the corporation, and, with respect to any criminal action or proceeding, if he or she had no reason to believe his or her conduct was unlawful. In a derivative action, (*i.e.*, one brought by or on behalf of the corporation), indemnification may be provided only for expenses actually and reasonably incurred by any director or officer in connection with the defense or settlement of such an action or suit if such person acted in good faith and in a manner that he or she reasonably believed to be in, or not opposed to, the best interests of the corporation, except that no indemnification shall be provided if such person shall have been adjudged to be liable to the corporation, unless and only to the extent that the court in which the action or suit was brought shall determine that the defendant is fairly and reasonably entitled to indemnity for such expenses despite such adjudication of liability.

Pursuant to Section 102(b)(7) of the DGCL, the Registrant's certificate of incorporation eliminates the liability of a director to the Registrant's stockholders for monetary damages for such a breach of fiduciary duty as a director, except

for liabilities arising:

from any breach of the director's duty of loyalty to the Registrant or the Registrant's stockholders;

from acts or omissions not in good faith or which involve intentional misconduct or a knowing violation of law;

under Section 174 of the DGCL; and

from any transaction from which the director derived an improper personal benefit.

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The Registrant has entered into agreements to indemnify the Registrant's directors and executive officers. These agreements, among other things, provide that the Registrant will indemnify the director or executive officer to the fullest extent authorized or permitted by the provisions of the Registrant's certificate of incorporation, bylaws or law for claims arising in his or her capacity as a director or officer of the Registrant. The indemnification agreements also establish the procedures that will apply in the event a director or officer makes a claim for indemnification.

The Registrant maintains a general liability insurance policy which covers certain liabilities of directors and officers of the Registrant arising out of claims based on acts or omissions in their capacities as directors or officers.

The foregoing discussion of the Registrant's certificate of incorporation, bylaws, indemnification agreements, and Delaware law is not intended to be exhaustive and is qualified in its entirety by such certificate of incorporation, bylaws, indemnification agreements, or law.

In any underwriting agreement the Registrant enters into in connection with the sale of common stock being registered hereby, the underwriters will agree to indemnify, under certain conditions, the Registrant, the Registrant's directors, the Registrant's officers and persons who control the Registrant with the meaning of the Securities Act of 1933 against certain liabilities.

### **Item 16. Exhibits.**

See the Exhibit Index on the page immediately preceding the exhibits for a list of exhibits filed as part of this Registration Statement, which Exhibit Index is incorporated herein by reference.

### **Item 17. Undertakings.**

The undersigned Registrant hereby undertakes:

(1) To file, during any period in which offers or sales are being made, a post-effective amendment to this Registration Statement:

(i) To include any prospectus required by Section 10(a)(3) of the Securities Act of 1933;

(ii) To reflect in the prospectus any facts or events arising after the effective date of the Registration Statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in the Registration Statement. Notwithstanding the foregoing, any increase or decrease in volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the SEC pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than 20 percent change in the maximum aggregate offering price set forth in the Calculation of Registration Fee table in the effective Registration Statement.

(iii) To include any material information with respect to the plan of distribution not previously disclosed in the Registration Statement or any material change to such information in the Registration Statement;

*provided, however,* that paragraphs (1)(i), (1)(ii) and (1)(iii) do not apply if the information required to be included in a post-effective amendment by those paragraphs is contained in reports filed with or furnished to the SEC by the



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Registrant pursuant to Section 13 or Section 15(d) of the Securities Exchange Act of 1934 that are incorporated by reference in the Registration Statement, or is contained in a form of prospectus filed pursuant to Rule 424(b) that is part of the Registration Statement.

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- (2) That, for the purpose of determining any liability under the Securities Act of 1933, each such post-effective amendment shall be deemed to be a new Registration Statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof.
- (3) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.
- (4) That, for the purpose of determining liability under the Securities Act of 1933 to any purchaser:
- (A) Each prospectus filed by the Registrant pursuant to Rule 424(b)(3) shall be deemed to be part of the Registration Statement as of the date the filed prospectus was deemed part of and included in the Registration Statement; and
- (B) Each prospectus required to be filed pursuant to Rule 424(b)(2), (b)(5), or (b)(7) as part of a Registration Statement in reliance on Rule 430B relating to an offering made pursuant to Rule 415(a)(1)(i), (vii), or (x) for the purpose of providing the information required by section 10(a) of the Securities Act of 1933 shall be deemed to be part of and included in the Registration Statement as of the earlier of the date such form of prospectus is first used after effectiveness or the date of the first contract of sale of securities in the offering described in the prospectus. As provided in Rule 430B, for liability purposes of the issuer and any person that is at that date an underwriter, such date shall be deemed to be a new effective date of the Registration Statement relating to the securities in the Registration Statement to which that prospectus relates, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof. *Provided, however,* that no statement made in a Registration Statement or prospectus that is part of the Registration Statement or made in a document incorporated or deemed incorporated by reference into the Registration Statement or prospectus that is part of the Registration Statement will, as to a purchaser with a time of contract of sale prior to such effective date, supersede or modify any statement that was made in the Registration Statement or prospectus that was part of the Registration Statement or made in any such document immediately prior to such effective date;
- (5) That, for the purpose of determining liability of the Registrant under the Securities Act of 1933 to any purchaser in the initial distribution of the securities, the undersigned Registrant undertakes that in a primary offering of securities of the undersigned Registrant pursuant to this Registration Statement, regardless of the underwriting method used to sell the securities to the purchaser, if the securities are offered or sold to such purchaser by means of any of the following communications, the undersigned Registrant will be a seller to the purchaser and will be considered to offer or sell such securities to such purchaser:
- (i) Any preliminary prospectus or prospectus of the undersigned Registrant relating to the offering required to be filed pursuant to Rule 424;
- (ii) Any free writing prospectus relating to the offering prepared by or on behalf of the undersigned Registrant or used or referred to by the undersigned Registrant;
- (iii) The portion of any other free writing prospectus relating to the offering containing material information about the undersigned Registrant or its securities provided by or on behalf of the undersigned Registrant; and
- (iv) Any other communication that is an offer in the offering made by the undersigned Registrant to the purchaser.
- (6) The undersigned Registrant hereby undertakes that, for purposes of determining any liability under the Securities Act of 1933, each filing of the Registrant's annual report pursuant to section 13(a) or section 15(d) of the Securities Exchange Act of 1934 (and, where applicable, each filing of an employee benefit plan's annual report pursuant to

section 15(d) of the Securities Exchange Act of 1934) that is incorporated by reference in the Registration Statement shall be deemed to be a new Registration Statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof.

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(7) That, for purposes of determining any liability under the Securities Act of 1933:

(i) the information omitted from the form of prospectus filed as part of the registration statement in reliance upon Rule 430A and contained in the form of prospectus filed by the registrant pursuant to Rule 424(b)(1) or (4) or 497(h) under the Securities Act of 1933 shall be deemed to be a part of the registration statement as of the time it was declared effective; and

(ii) each post-effective amendment that contains a form of prospectus shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

Insofar as indemnification for liabilities arising under the Securities Act of 1933 may be permitted to directors, officers and controlling persons of the Registrant pursuant to the foregoing provisions, or otherwise, the Registrant has been advised that in the opinion of the SEC such indemnification is against public policy as expressed in the Securities Act of 1933 and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the Registrant of expenses incurred or paid by a director, officer or controlling person of the Registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the Registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act of 1933 and will be governed by the final adjudication of such issue.

Table of Contents**SIGNATURES**

Pursuant to the requirements of the Securities Act of 1933, as amended, the Registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this Registration Statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of San Diego, State of California, on April 29, 2016.

**REGULUS THERAPEUTICS INC.**

By: /s/ Paul C. Grint  
Paul C. Grint, M.D.

*President and Chief Executive Officer*

Pursuant to the requirements of the Securities Act of 1933, as amended, this Registration Statement has been signed by the following persons in the capacities and on the dates indicated.

| <b>Signature</b>                         | <b>Title</b>   | <b>Date</b>    |
|--|--|----------------|
| /s/ Paul C. Grint<br>Paul C. Grint, M.D. | President, Chief Executive Officer and<br>Member of the Board of Directors<br><br><i>(Principal Executive Officer)</i> | April 29, 2016 |
| /s/ Joseph P. Hagan<br>Joseph P. Hagan   | Chief Operating Officer<br><br><i>(Principal Financial and Accounting Officer)</i>                                     | April 29, 2016 |
| *<br>David Baltimore, Ph.D.              | Member of the Board of Directors   | April 29, 2016 |
| *<br>Mark G. Foletta                     | Member of the Board of Directors   | April 29, 2016 |
| *<br>Stelios Papadopoulos, Ph.D.         | Member of the Board of Directors   | April 29, 2016 |
| *<br>William H. Rastetter, Ph.D.         | Member of the Board of Directors   | April 29, 2016 |
| *<br>Douglas E. Williams, Ph.D.          | Member of the Board of Directors   | April 29, 2016 |

\* By: /s/ Paul C. Grint  
Paul C. Grint, M.D.

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**Table of Contents****EXHIBIT INDEX**

| <b>Exhibit<br/>Number</b> | <b>Description</b>   |
|---------------------------|--|
| 1.1                       | Form of Underwriting Agreement (to be filed by amendment or as an exhibit to a current report on Form 8-K of the Registrant, and incorporated herein by reference).  |
| 4.1                       | Amended and Restated Certificate of Incorporation of the Registrant (incorporated by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K, filed with the SEC on October 11, 2012).   |
| 4.2                       | Amended and Restated Bylaws of the Registrant (incorporated by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K, filed with the SEC on December 5, 2014).   |
| 4.3                       | Form of Common Stock Certificate of the Registrant (incorporated by reference to Exhibit 4.1 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-183384), originally filed with the SEC on August 17, 2012).                          |
| 4.4                       | Registration Rights Agreement dated February 5, 2014 between the Registrant and Aventisub LLC (formerly Aventis Holdings Inc.) (incorporated by reference to Exhibit 99.3 to the Registrant's Current Report on Form 8-K, filed with the SEC on February 5, 2014). |
| 5.1                       | Opinion of Cooley LLP (incorporated by reference to Exhibit 5.1 to the Registrant's Post-Effective Amendment No. 1 to the Registration Statement on Form S-3 (File No. 333-203292), filed with the SEC on February 23, 2016).                                      |
| 23.1                      | Consent of Independent Registered Public Accounting Firm.  |
| 23.2                      | Consent of Cooley LLP (included in Exhibit 5.1).   |
| 24.1                      | Power of Attorney (previously filed with the SEC).   |