

Regulus Therapeutics Inc.
Form 424B5
July 19, 2017
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The information in this preliminary prospectus supplement 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 preliminary prospectus supplement and the accompanying prospectus are not an offer to sell these securities, and we are not soliciting offers to buy these securities, in any state or other jurisdiction where the offer or sale is not permitted.

**Filed Pursuant to Rule 424(b)(5)
Registration No. 333-203292**

SUBJECT TO COMPLETION, DATED JULY 19, 2017

PRELIMINARY PROSPECTUS SUPPLEMENT

(To Prospectus dated May 2, 2016)

Shares

Common Stock

We are offering _____ shares of our common stock. Our common stock is listed on The NASDAQ Global Market under the symbol RGLS. On July 18, 2017, the last sale price of our common stock as reported on The NASDAQ Global Market was \$0.946 per share.

We are an emerging growth company as that term is used in the Jumpstart Our Business Startups Act of 2012 and, as such, have elected to comply with certain reduced public company reporting requirements for this prospectus supplement and future filings.

Investing in our common stock involves significant risks. Please read Risk Factors on page S-4 of this prospectus supplement and the documents incorporated by reference into this prospectus supplement.

	Per Share	Total
Public offering price	\$	\$
Underwriting discounts and commissions ⁽¹⁾	\$	\$
Proceeds, before expenses, to us	\$	\$

(1) See Underwriting for a description of the compensation payable to the underwriters.

We have granted the underwriters an option to purchase up to an additional _____ shares at the public offering price, less the underwriting discounts and commissions, for a period of 30 days following the date of this prospectus supplement. If the underwriters exercise in full their option, the total underwriting discounts and commissions payable by us will be \$ _____, and the total proceeds to us, before expenses, will be \$ _____.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved these securities or determined if this prospectus supplement or the accompanying prospectus is accurate or complete. Any representation to the contrary is a criminal offense.

The underwriters expect to deliver the shares to purchasers on or before July _____, 2017.

Sole Book-Running Manager

Leerink Partners

Prospectus Supplement dated July _____, 2017

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Prospectus

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We have not, and the underwriters have not, authorized anyone to provide you with different information than that which is contained in or incorporated by reference in this prospectus supplement, the accompanying prospectus and in any free writing prospectus that we have authorized for use in connection with this offering. We are not, and the underwriters are not, making an offer to sell these securities in any jurisdiction where the offer or sale is not permitted. You should assume that the information appearing in this prospectus supplement, the accompanying prospectus, the documents incorporated by reference into this prospectus supplement and the accompanying prospectus, and in any free writing prospectus that we have authorized for

use in connection with this offering, is accurate only as of the date of those respective documents. Our business, financial condition, results of operations and prospects may have changed since those dates. You should read this prospectus supplement, the accompanying prospectus, the documents incorporated by reference into this prospectus supplement and the accompanying prospectus, and any free writing prospectus that we have authorized for use in connection with this offering, in their entirety before making an investment decision. You should also read and consider the information in the documents to which we have referred you in the sections of this prospectus supplement entitled **Where You Can Find More Information and **Incorporation of Certain Information by Reference**.**

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ABOUT THIS PROSPECTUS SUPPLEMENT

This document is in two parts. The first part is this prospectus supplement, which describes the terms of this offering of common stock and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus. The second part, the accompanying prospectus dated May 2, 2016, including the documents incorporated by reference therein, provides more general information. Generally, when we refer to this prospectus, we are referring to both parts of this document combined. To the extent there is a conflict between the information contained in this prospectus supplement, on the one hand, and the information contained in the accompanying prospectus or in any document incorporated by reference that was filed with the Securities and Exchange Commission, or SEC, before the date of this prospectus supplement, on the other hand, you should rely on the information in this prospectus supplement. If any statement in one of these documents is inconsistent with a statement in another document having a later date for example, a document incorporated by reference into this prospectus or the accompanying prospectus the statement in the document having the later date modifies or supersedes the earlier statement. You should assume that the information contained in this prospectus supplement is accurate as of the date on the front cover of this prospectus supplement only and that any information we have incorporated by reference or included in the accompanying prospectus is accurate only as of the date given in the document incorporated by reference or as of the date of the prospectus, as applicable, regardless of the time of delivery of this prospectus supplement or the accompanying prospectus or any sale of our common stock. Our business, financial condition, results of operations and prospects may have changed since that date.

In this prospectus supplement, unless otherwise stated or the context otherwise requires, the terms Regulus, the Company, we, us and our refer to Regulus Therapeutics Inc.

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PROSPECTUS SUPPLEMENT SUMMARY

*This summary highlights selected information contained elsewhere or incorporated by reference in this prospectus supplement and the accompanying prospectus. This summary does not contain all the information you should consider before investing in our common stock. You should read and consider carefully the more detailed information in this prospectus supplement and the accompanying prospectus, including the factors described under the heading **Risk Factors** in this prospectus supplement on page S-4 and the financial and other information contained in or incorporated by reference into this prospectus supplement and the accompanying prospectus, as well as the information included in any free writing prospectus that we have authorized for use in connection with this offering, before making an investment decision.*

The Company

We are a clinical-stage biopharmaceutical company focused on discovering and developing first-in-class drugs targeting microRNAs to treat diseases with significant unmet medical need. We were formed in 2007 when Alnylam Pharmaceuticals, Inc. and Ionis Pharmaceuticals, Inc. 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. Our most advanced program, under our strategic alliance with Sanofi, is RG-012, an anti-miR targeting miR-21 for the treatment of Alport syndrome, a life-threatening kidney disease driven by genetic mutations, currently with no approved therapy available.

microRNAs are naturally occurring ribonucleic acid, or RNA, molecules that play a critical role in regulating key biological pathways. Scientific research has shown that an imbalance, or dysregulation, of *microRNAs* is directly linked to many diseases. Furthermore, many different infectious pathogens interact and bind to host microRNA to survive. To date, over 500 *microRNAs* have been identified in humans, each of which can bind to multiple messenger RNAs that control key aspects of cell biology. Since many diseases are multi-factorial, involving multiple targets and pathways, the ability to modulate multiple pathways by targeting a single *microRNA* provides a new therapeutic approach for treating complex diseases.

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 are using our *microRNA* expertise to develop chemically modified, single-stranded oligonucleotides that we call anti-miRs to modulate *microRNAs* and address underlying disease. We believe *microRNAs* may play a critical role in complex disease and that targeting them with anti-miRs may become a source of a new and major class of drugs with broad therapeutic application, much like small molecules, biologics and monoclonal antibodies.

Preliminary Cash Position as of June 30, 2017

Our cash, cash equivalents and short-term investments were approximately \$40.1 million as of June 30, 2017. This financial result is preliminary and unaudited and may differ from what will be reflected in our condensed financial statements as of and for the quarter ended June 30, 2017. Our condensed financial statements as of and for the quarter ended June 30, 2017 will not be available until after this offering is complete, and consequently will not be available to you prior to investing in this offering.

Corporate Information

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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

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10614 Sciences Center Drive, San Diego, California 92121, and our telephone number is (858) 202-6300. Our corporate website address is www.regulusrx.com. Information contained on or accessible through our website is not a part of this prospectus supplement or the accompanying prospectus, and the inclusion of our website address in this prospectus supplement is an inactive textual reference only.

The Regulus Therapeutics logo is a trademark of Regulus Therapeutics Inc. We use Regulus Therapeutics as a trademark in the United States and other countries and have registered this trademark in the United States. We use *microMarkers* as a servicemark in the United States and other countries and have registered this servicemark in the United States. This prospectus supplement 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 earliest of (a) December 31, 2017, (b) the last day of the fiscal year in which we have total annual gross revenue of at least \$1.07 billion, (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 or (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.

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The Offering

Common stock offered by us	shares
Common stock to be outstanding immediately after this offering	shares (or shares if the underwriters exercise in full their option to purchase additional shares)
Option to purchase additional shares	We have granted the underwriters an option to purchase up to an aggregate of additional shares of our common stock. This option is exercisable, in whole or in part, for a period of 30 days following the date of this prospectus supplement.
Use of proceeds	We intend to use the net proceeds of this offering to fund clinical development of our clinical candidates, RG-012 and RGLS4326, development of our earlier <i>microRNA</i> development candidates and programs, for the identification and validation of additional <i>microRNA</i> targets, and for capital expenditures, working capital and general corporate purposes. We may also use a portion of the net proceeds to in-license, acquire or invest in complementary <i>microRNA</i> businesses, technologies, products or assets. However, we have no current commitments or obligations to do so. See the section entitled Use of Proceeds .
Risk factors	Investing in our common stock involves significant risks. See Risk Factors on page S-4.
NASDAQ Global Market symbol	Our common stock is listed on The NASDAQ Global Market under the symbol RGLS.
The number of shares of our common stock to be outstanding immediately after this offering is based on 53,182,330 shares outstanding as of March 31, 2017. The number of shares excludes, as of March 31, 2017:	
	10,030,972 shares of common stock issuable upon the exercise of outstanding stock options under our equity incentive plans, with a weighted average exercise price of \$5.77 per share;
	1,728,217 shares of common stock available for future grants under our 2012 equity incentive plan; and
	1,844,527 shares of common stock available for issuance under our employee stock purchase plan.

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Except as otherwise indicated, all information in this prospectus supplement assumes no exercise by the underwriters of their option to purchase additional shares.

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RISK FACTORS

Investing in our common stock involves significant risks. Our business, prospects, financial condition and operating results could be materially adversely affected by the risks identified below or incorporated by reference herein, as well as other risks not currently known to us or that we currently consider immaterial. The trading price of our common stock could decline due to any of these risks, and you may lose all or part of your investment. You should consider carefully the risks described below and discussed in our Current Report on Form 8-K filed on July 19, 2017, which is incorporated by reference in this prospectus supplement in its entirety, together with the information contained in the other documents incorporated by reference into this prospectus supplement and the accompanying prospectus in their entirety, and other documents that we file from time to time with the SEC.

Risks Related to This Offering

Management will have broad discretion as to the use of the proceeds from this offering, and we may not use the proceeds effectively.

Our management will have broad discretion in the application of the net proceeds we receive from this offering, including for any of the purposes described in the section entitled Use of Proceeds, and you will not have the opportunity as part of your investment decision to assess whether the net proceeds are being used appropriately. Because of the number and variability of factors that will determine our use of the net proceeds from this offering, their ultimate use may vary substantially from their currently intended use. Our management could spend the proceeds in ways that do not improve our results of operations or enhance the value of our common stock. Our failure to apply these funds effectively could have a material adverse effect on our business, delay the development of our product candidates and cause the price of our common stock to decline.

If you purchase the common stock sold in this offering, you will experience immediate and substantial dilution in your investment. You will experience further dilution if we issue additional equity securities in future fundraising transactions.

Since the price per share of our common stock being offered is substantially higher than the net tangible book value per share of our common stock, you will suffer substantial dilution with respect to the net tangible book value of the common stock you purchase in this offering. Based on a public offering price of \$ per share and our net tangible book value as of March 31, 2017, if you purchase shares of common stock in this offering, you will suffer immediate and substantial dilution of \$ per share with respect to the net tangible book value of our common stock. See the section of this prospectus supplement entitled Dilution for a more detailed discussion of the dilution you will incur if you purchase common stock in this offering.

In addition, we have a significant number of stock options outstanding. To the extent that outstanding stock options have been or may be exercised or other securities issued, investors purchasing our common stock in this offering may experience further dilution. In addition, we may choose to raise additional capital due to market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. To the extent that additional capital is raised through the sale of equity or convertible debt securities, the issuance of these securities could result in further dilution to our stockholders or result in downward pressure on the price of our common stock.

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or 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, may, plan, 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 of any programs or product candidates that are subject to our collaboration and license agreements with such partners;

our ability to attract collaborators with relevant 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;

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 ability to satisfy our debt obligations;

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

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our use of the proceeds from this offering; and

the accuracy of our estimates regarding future 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. See the section of this prospectus supplement entitled **Risk Factors** for more information about factors that could cause actual results or events to differ from those contained in the forward-looking statements we make. You should consider these factors and other cautionary statements made in this prospectus supplement, the accompanying prospectus and in the documents we incorporate by reference as being applicable to all related forward-looking statements wherever they appear in this prospectus supplement, the accompanying 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.

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USE OF PROCEEDS

We estimate the net proceeds to us from the shares offered by us in this offering will be approximately \$ million (or \$ million if the underwriters exercise in full their option to purchase additional shares), after payment of estimated underwriting discounts and commissions and estimated offering expenses payable by us.

We intend to use the net proceeds from the shares sold in this offering for general corporate purposes, including clinical development of our clinical candidates, RG-012 and RGLS4326, development of our earlier *microRNA* development candidates and programs, for the identification and validation of additional *microRNA* targets, 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 cannot currently allocate specific percentages of the net proceeds to us from this offering that we may use for the purposes specified above and our management will have broad discretion in the allocation of the net proceeds. Pending their use, we plan to invest the net proceeds to us 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.

Table of Contents**DILUTION**

Our net tangible book value as of March 31, 2017 was approximately \$37.8 million, or \$0.71 per share. Net tangible book value per share is determined by dividing our total tangible assets, less total liabilities, by the number of shares of our common stock outstanding as of March 31, 2017. Dilution with respect to net tangible book value per share represents the difference between the amount per share paid by purchasers of shares of common stock in this offering and the net tangible book value per share of our common stock immediately after this offering.

After giving effect to the sale of _____ shares of our common stock by us in this offering at the public offering price of \$ _____ per share and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us, our as adjusted net tangible book value as of March 31, 2017 would have been approximately \$ _____ million, or \$ _____ per share. This represents an immediate increase in net tangible book value of \$ _____ per share to existing stockholders and immediate dilution in value of \$ _____ per share to investors purchasing common stock in this offering.

The following table illustrates this dilution on a per share basis:

Public offering price per share	\$
Net tangible book value per share as of March 31, 2017	\$ 0.71
Increase in net tangible book value per share attributable to new investors purchasing our common stock in this offering	

As adjusted net tangible book value per share on March 31, 2017, after giving effect to this offering

Dilution per share to new investors purchasing our common stock in this offering	\$
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If the underwriters exercise in full their option to purchase up to additional _____ shares of common stock in this offering at the public offering price of \$ _____ per share, the as adjusted net tangible book value after this offering would have been \$ _____ per share, representing an increase in net tangible book value of \$ _____ per share to existing stockholders and immediate dilution in value of \$ _____ per share to investors purchasing common stock in this offering at the public offering price.

The above discussion and table are based on 53,182,330 shares outstanding as of March 31, 2017, and exclude as of that date:

10,030,972 shares of common stock issuable upon the exercise of outstanding stock options under our equity incentive plans, with a weighted average exercise price of \$5.77 per share;

1,728,217 shares of common stock available for future grants under our 2012 equity incentive plan; and

1,844,527 shares of common stock available for issuance under our employee stock purchase plan.

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To the extent that stock options outstanding as of March 31, 2017 have been or may be exercised or other securities issued, investors purchasing our common stock in this offering may experience further dilution. In addition, we may choose to raise additional capital due to market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. To the extent that additional capital is raised through the sale of equity or convertible debt securities, the issuance of these securities could result in further dilution to our stockholders.

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**MATERIAL U.S. FEDERAL INCOME TAX CONSEQUENCES TO
NON-U.S. HOLDERS OF OUR COMMON STOCK**

The following is a discussion of the material U.S. federal income tax consequences to non-U.S. holders (as defined below) with respect to their purchase, ownership and disposition of shares of our common stock issued pursuant to this offering, but does not purport to be a complete analysis of all potential tax effects. All prospective non-U.S. holders of our common stock should consult their own tax advisors with respect to the U.S. federal income tax consequences of the purchase, ownership and disposition of our common stock, as well as any consequences arising under the laws of any other taxing jurisdiction, including any state, local and non-U.S. tax consequences and any U.S. federal non-income tax consequences. In general, a non-U.S. holder means a beneficial owner of our common stock (other than a partnership or an entity or arrangement treated as a partnership for U.S. federal income tax purposes) that is not, for U.S. federal income tax purposes:

an individual who is a citizen or resident of the United States;

a corporation, or an entity treated as a corporation for U.S. federal income tax purposes, created or organized in the United States or under the laws of the United States or of any state thereof or the District of Columbia;

an estate, the income of which is subject to U.S. federal income tax regardless of its source; or

a trust if (1) a U.S. court can exercise primary supervision over the trust's administration and one or more United States persons have the authority to control all of the trust's substantial decisions or (2) the trust has a valid election in effect under applicable U.S. Treasury Regulations to be treated as a United States person.

This discussion is based on current provisions of the U.S. Internal Revenue Code of 1986, as amended, which we refer to as the Code, existing U.S. Treasury Regulations promulgated thereunder, published administrative rulings and judicial decisions, all as in effect as of the date of this prospectus supplement. These laws are subject to change and to differing interpretation, possibly with retroactive effect. Any change or differing interpretation could alter the tax consequences to non-U.S. holders described in this prospectus supplement.

This discussion is limited to non-U.S. holders that hold shares of our common stock as a capital asset within the meaning of Section 1221 of the Code (generally, property held for investment). This discussion does not address all aspects of U.S. federal income taxation that may be relevant to a particular non-U.S. holder in light of that non-U.S. holder's individual circumstances, nor does it address any aspects of U.S. estate or gift tax, or any state, local or non-U.S. taxes. This discussion also does not consider any specific facts or circumstances that may apply to a non-U.S. holder and does not address the special tax rules applicable to particular non-U.S. holders, such as holders that own, or are deemed to own, more than 5% of our capital stock (except to the extent specifically set forth below), tax-exempt organizations, foreign governments, international organizations, banks, financial institutions, insurance companies, brokers, dealers or traders in securities, commodities or currencies, tax-qualified retirement plans, holders subject to the alternative minimum tax or Medicare contribution tax, holders who hold or receive our common stock pursuant to the exercise of employee stock options or otherwise as compensation, holders holding our common stock as part of a hedge, straddle or other risk reduction strategy, conversion transaction or other integrated investment, holders deemed to sell our common stock under the constructive sale provisions of the Code, controlled foreign

corporations, passive foreign investment companies, corporations that accumulate earnings to avoid U.S. federal income tax, qualified foreign pension funds as defined in Section 897(1)(2) of the Code and entities all of the interests of which are held by qualified foreign pension funds, and U.S. expatriates and certain former citizens or long-term residents of the United States.

In addition, this discussion does not address the tax treatment of partnerships (or entities or arrangements that are treated as partnerships for U.S. federal income tax purposes) or persons that hold their common stock through such partnerships or such entities or arrangements. If a partnership, including any entity or arrangement

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treated as a partnership for U.S. federal income tax purposes, holds shares of our common stock, the U.S. federal income tax treatment of a partner in such partnership will generally depend upon the status of the partner, the activities of the partnership and certain determinations made at the partner level. Such partners and partnerships should consult their own tax advisors regarding the tax consequences of the purchase, ownership and disposition of our common stock.

There can be no assurance that the Internal Revenue Service, which we refer to as the IRS, will not challenge one or more of the tax consequences described herein, and we have not obtained, nor do we intend to obtain, a ruling with respect to the U.S. federal income tax consequences with respect to the matters discussed below.

Distributions on Our Common Stock

Distributions, if any, on our common stock generally will constitute dividends for U.S. federal income tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. If a distribution exceeds our current and accumulated earnings and profits, the excess will be treated as a tax-free return of the non-U.S. holder's investment, up to such holder's adjusted tax basis in the common stock. Any remaining excess will be treated as capital gain from the sale or exchange of such common stock, subject to the tax treatment described below in [Gain on Sale, Exchange or Other Disposition of Our Common Stock](#).

The gross amount of the dividends paid to a non-U.S. holder will generally be subject to withholding of U.S. federal income tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty. A non-U.S. holder of our common stock who claims the benefit of an applicable income tax treaty generally will be required to provide a properly executed IRS Form W-8BEN or W-8BEN-E (or successor forms) and satisfy relevant certification and other requirements. Non-U.S. holders are urged to consult their tax advisors regarding their entitlement to benefits under a relevant income tax treaty. Non-U.S. holders should consult their own tax advisors to determine whether they may be eligible for a reduced rate of U.S. withholding tax under an income tax treaty, including whether they may obtain a refund or credit of any excess amounts withheld by timely filing an appropriate claim for refund with the IRS.

Dividends that are treated as effectively connected with a trade or business conducted by a non-U.S. holder within the United States and, if an applicable income tax treaty so provides, that are attributable to a permanent establishment or a fixed base maintained by the non-U.S. holder within the United States, are generally exempt from the 30% withholding tax if the non-U.S. holder satisfies applicable certification and disclosure requirements. To claim the exemption, the non-U.S. holder must furnish to us or our paying agent a valid IRS Form W-8ECI (or applicable successor form), certifying that the dividends are effectively connected with the non-U.S. holder's conduct of a trade or business within the United States. However, such U.S. effectively connected income, net of specified deductions and credits, is taxed at the same graduated U.S. federal income tax rates applicable to United States persons (as defined in the Code), unless a specific treaty exemption applies. Any U.S. effectively connected income received by a non-U.S. holder that is a corporation may also, under certain circumstances, be subject to an additional branch profits tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty.

Dividends may be subject to withholding as described below in [Backup Withholding and Information Reporting](#) and [Foreign Accounts](#).

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Gain on Sale, Exchange or Other Disposition of Our Common Stock

Subject to the discussion below regarding backup withholding and under **Foreign Accounts**, in general, a non-U.S. holder will not be subject to any U.S. federal income tax on any gain realized upon such holder's sale, exchange or other disposition of shares of our common stock unless:

the gain is effectively connected with a U.S. trade or business of the non-U.S. holder and, if an applicable income tax treaty so provides, is attributable to a permanent establishment or a fixed base maintained in the United States by such non-U.S. holder, in which case the non-U.S. holder generally will be taxed at the graduated U.S. federal income tax rates applicable to United States persons (as defined in the Code) and, if the non-U.S. holder is a corporation, the branch profits tax described above in **Distributions on Our Common Stock** may also apply;

the non-U.S. holder is a nonresident alien individual who is present in the United States for 183 days or more in the taxable year of the disposition and certain other conditions are met, in which case the non-U.S. holder will be subject to a 30% tax (or such lower rate as may be specified by an applicable income tax treaty) on the net gain derived from the disposition, which may be offset by U.S. source capital losses of the non-U.S. holder, if any (even though the individual is not considered a resident of the United States), provided the non-U.S. holder has timely filed U.S. federal income tax returns with respect to such losses; or

our common stock constitutes a U.S. real property interest because we are, or have been, at any time during the five-year period preceding such disposition (or the non-U.S. holder's holding period, if shorter) a U.S. real property holding corporation. Even if we are or become a U.S. real property holding corporation, provided that our common stock is regularly traded on an established securities market, our common stock will be treated as a U.S. real property interest only with respect to a non-U.S. holder that holds more than 5% of our outstanding common stock, directly or indirectly, actually or constructively, during the shorter of the 5-year period ending on the date of the disposition or the period that the non-U.S. holder held our common stock. In such case, such non-U.S. holder generally will be taxed on its net gain derived from the disposition at the graduated U.S. federal income tax rates applicable to United States persons (as defined in the Code). Generally, a corporation is a U.S. real property holding corporation only if the fair market value of its U.S. real property interests equals or exceeds 50% of the sum of the fair market value of its worldwide real property interests plus its other assets used or held for use in a trade or business. Although there can be no assurance, we do not believe that we are, or have been, a U.S. real property holding corporation, or that we are likely to become one in the future. No assurance can be provided that our common stock will be regularly traded on an established securities market for purposes of the rules described above.

Backup Withholding and Information Reporting

We or certain financial middlemen must report annually to the IRS and to each non-U.S. holder the gross amount of the dividends on our common stock paid to such holder and the tax withheld, if any, with respect to such dividends. Non-U.S. holders will have to comply with specific certification procedures to establish that the holder is not a United States person (as defined in the Code) in order to avoid backup withholding at the applicable rate with respect to dividends on our common stock. U.S. backup withholding generally will not apply to a non-U.S. holder with respect to dividends on our common stock, provided the holder certifies its status as a non-U.S. holder, such as by providing a properly executed IRS Form W-8BEN, W-8BEN-E or W-8ECI, and the applicable withholding agent does not have

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actual knowledge or reason to know the holder is a United States person, or the holder otherwise establishes an exemption.

Information reporting and backup withholding will generally apply to the proceeds of a disposition of our common stock by a non-U.S. holder effected by or through the U.S. office of any broker, U.S. or foreign, unless the holder certifies its status as a non-U.S. holder, such as by providing a properly executed IRS Form W-8BEN, W-8BEN-E or W-8ECI, and the applicable withholding agent does not have actual knowledge or reason to know

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the holder is a United States person, or the holder otherwise establishes an exemption. Generally, information reporting and backup withholding will not apply to a payment of disposition proceeds to a non-U.S. holder where the transaction is effected outside the United States through a non-U.S. office of a broker. However, for information reporting purposes, dispositions effected through a non-U.S. office of a broker with certain U.S. ownership or operations generally will be treated in a manner similar to dispositions effected through a U.S. office of a broker. Non-U.S. holders should consult their own tax advisors regarding the application of the information reporting and backup withholding rules.

Copies of information returns may be made available to the tax authorities of the country in which the non-U.S. holder resides or is incorporated under the provisions of a specific treaty or agreement.

Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules from a payment to a non-U.S. holder may be allowed as a credit against the non-U.S. holder's U.S. federal income tax liability, if any, and may entitle such holder to a refund, provided that the required information is timely furnished to the IRS.

Foreign Accounts

The Code generally imposes a U.S. federal withholding tax of 30% on dividends and the gross proceeds of a disposition of our common stock paid to a foreign financial institution or a non-financial foreign entity (as specifically defined for this purpose in the Code), unless (1) the foreign financial institution undertakes certain diligence and reporting obligations, (2) the non-financial foreign entity either certifies it does not have any substantial United States owners (as defined in the Code) or furnishes identifying information regarding each substantial United States owner, or (3) the foreign financial institution or non-financial foreign entity otherwise qualifies for an exemption from these rules. If the foreign financial institution is subject to the diligence and reporting requirements, such institution must enter into an agreement with the U.S. government to, among other things, withhold on certain payments and to collect and provide to the U.S. tax authorities substantial information regarding U.S. account holders of such institution (which may include certain equity and debt holders of such institution, as well as certain account holders that are foreign entities with U.S. owners). Foreign financial institutions located in jurisdictions that have an intergovernmental agreement with the United States governing these withholding and reporting requirements may be subject to different rules. This U.S. federal withholding tax of 30% also applies to dividends and the gross proceeds of a disposition of our common stock paid to a non-financial foreign entity, unless such entity provides the withholding agent with either a certification that it does not have any substantial direct or indirect U.S. owners or provides information regarding substantial direct and indirect U.S. owners of the entity. The withholding tax described above will not apply if the foreign financial institution or non-financial foreign entity otherwise qualifies for an exemption from the rules. This U.S. federal withholding tax currently applies to dividends on our common stock and will generally apply to gross proceeds of a sale or other disposition of our common stock on or after January 1, 2019. Non-U.S. holders are encouraged to consult their own tax advisors regarding the possible implications of these U.S. federal withholding tax rules in relation to their investment in our common stock.

EACH PROSPECTIVE INVESTOR SHOULD CONSULT ITS OWN TAX ADVISOR REGARDING THE TAX CONSEQUENCES OF PURCHASING, OWNING AND DISPOSING OF OUR COMMON STOCK AS WELL AS TAX CONSEQUENCES ARISING UNDER ANY STATE, LOCAL, NON-U.S. OR U.S. FEDERAL NON-INCOME TAX LAWS.

Table of Contents**UNDERWRITING**

Leerink Partners LLC is acting as representative of each of the underwriters named below and as sole book-running manager for this offering. Subject to the terms and conditions set forth in the underwriting agreement among us and the underwriters, we have agreed to sell to the underwriters, and each of the underwriters has agreed, severally and not jointly, to purchase from us, the number of shares of common stock set forth opposite its name below.

Underwriter	Number of Shares
Leerink Partners LLC	
Total	

Subject to the terms and conditions set forth in the underwriting agreement, the underwriters have agreed, severally and not jointly, to purchase all of the shares sold under the underwriting agreement if any of the shares are purchased. If an underwriter defaults, the underwriting agreement provides that the purchase commitments of the non-defaulting underwriters may be increased or the underwriting agreement may be terminated.

We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act, or to contribute to payments the underwriters may be required to make in respect of those liabilities.

The underwriters are offering the shares, subject to prior sale, when, as and if issued to and accepted by them, subject to approval of legal matters by their counsel, including the validity of the shares, and other conditions contained in the underwriting agreement, such as the receipt by the underwriters of officers' certificates and legal opinions. The underwriters reserve the right to withdraw, cancel or modify offers to the public and to reject orders in whole or in part.

Commissions and Discounts

The representative has advised us that the underwriters propose initially to offer the shares to the public at the public offering price set forth on the cover page of this prospectus and to dealers at that price less a concession not in excess of \$ per share. After the initial offering of the shares, the public offering price, concession or any other term of the offering may be changed by the representative.

The following table shows the public offering price, underwriting discounts and commissions and proceeds before expenses to us. The information assumes either no exercise or full exercise by the underwriters of their option to purchase additional shares of our common stock.

	Per Share	Total	
		Without Option	With Option
Public offering price	\$	\$	\$
Underwriting discounts and commissions	\$	\$	\$
Proceeds, before expenses, to us	\$	\$	\$

We estimate expenses payable by us in connection with this offering, other than the underwriting discounts and commissions referred to above, will be approximately \$300,000. We also have agreed to reimburse the underwriters

for up to \$10,000 for their FINRA counsel fee. In accordance with FINRA Rule 5110, this reimbursed fee is deemed underwriting compensation for this offering.

Option to Purchase Additional Shares

We have granted an option to the underwriters, exercisable for 30 days after the date of this prospectus, to purchase up to an additional _____ shares at the public offering price, less the underwriting discounts

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and commissions. If the underwriters exercise this option, each underwriter will be obligated, subject to conditions contained in the underwriting agreement, to purchase a number of additional shares proportionate to that underwriter's initial amount reflected in the above table.

No Sales of Similar Securities

We and each of our executive officers and directors have agreed not to sell or transfer any common stock or securities convertible into or exchangeable or exercisable for common stock, for 90 days after the date of this prospectus without first obtaining the written consent of Leerink Partners LLC on behalf of the underwriters, subject to specified exceptions. Specifically, we and these other persons have agreed, with certain limited exceptions, not to directly or indirectly:

offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, lend, or otherwise transfer or dispose of, any shares of common stock or any securities convertible into or exercisable or exchangeable for common stock or publicly disclose the intention to do any of the foregoing;

enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of our common stock or publicly disclose the intention to do any of the foregoing; or

make any demand for or exercise any right with respect to, the registration of any shares of common stock or any security convertible into or exercisable or exchangeable for common stock.

NASDAQ Global Market Listing

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

Price Stabilization, Short Positions and Penalty Bids

Until the distribution of the shares is completed, SEC rules may limit underwriters and selling group members from bidding for and purchasing our common stock. However, the representative may engage in transactions that stabilize the price of the common stock, such as bids or purchases to peg, fix or maintain that price.

In connection with the offering, the underwriters may purchase and sell our common stock in the open market. These transactions may include short sales, purchases on the open market to cover positions created by short sales and stabilizing transactions. Short sales involve the sale by the underwriters of a greater number of shares than they are required to purchase in the offering. Covered short sales are sales made in an amount not greater than the underwriters' option described above. The underwriters may close out any covered short position by either exercising their option or purchasing shares in the open market. In determining the source of shares to close out the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase shares through the option granted to them. Naked short sales are sales in excess of such option. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of our common stock in the open market after pricing that could adversely affect

investors who purchase in the offering. Stabilizing transactions consist of various bids for or purchases of shares of common stock made by the underwriters in the open market prior to the closing of the offering.

The underwriters may also impose a penalty bid. This occurs when a particular underwriter repays to the underwriters a portion of the underwriting discount received by it because the representative has repurchased shares sold by or for the account of such underwriter in stabilizing or short covering transactions.

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Similar to other purchase transactions, the underwriters' purchases to cover the syndicate short sales may have the effect of raising or maintaining the market price of our common stock or preventing or retarding a decline in the market price of our common stock. As a result, the price of our common stock may be higher than the price that might otherwise exist in the open market. The underwriters may conduct these transactions on The NASDAQ Global Market, in the over-the-counter market or otherwise.

Neither we nor any of the underwriters make any representation or prediction as to the direction or magnitude of any effect that the transactions described above may have on the price of our common stock. In addition, neither we nor any of the underwriters make any representation that the representative will engage in these transactions or that these transactions, once commenced, will not be discontinued without notice.

The underwriters may also engage in passive market making transactions in our common stock on The NASDAQ Global Market in accordance with Rule 103 of Regulation M during a period before the commencement of offers or sales of shares of our common stock in this offering and extending through the completion of distribution. A passive market maker must display its bid at a price not in excess of the highest independent bid of that security. However, if all independent bids are lowered below the passive market maker's bid, that bid must then be lowered when specified purchase limits are exceeded.

Electronic Distribution

In connection with the offering, certain of the underwriters or securities dealers may distribute prospectuses by electronic means, such as e-mail.

Other Relationships

The underwriters and certain of their affiliates are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, investment research, principal investment, hedging, financing and brokerage activities. Some of the underwriters and certain of their affiliates may in the future engage in investment banking and other commercial dealings in the ordinary course of business with us and our affiliates, for which they may in the future receive customary fees, commissions and expenses.

In addition, in the ordinary course of their business activities, the underwriters and their affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (including bank loans) for their own account and for the accounts of their customers. Such investments and securities activities may involve securities and/or instruments of ours or our affiliates. The underwriters and their affiliates may also make investment recommendations and/or publish or express independent research views in respect of such securities or financial instruments and may hold, or recommend to clients that they acquire, long and/or short positions in such securities and instruments.

Notice to Prospective Investors in the European Economic Area

In relation to each member state of the European Economic Area that has implemented the Prospectus Directive (each, a relevant member state), with effect from and including the date on which the Prospectus Directive is implemented in that relevant member state (the relevant implementation date), an offer of shares described in this prospectus supplement may not be made to the public in that relevant member state other than:

to any legal entity which is a qualified investor as defined in the Prospectus Directive;

to fewer than 100 or, if the relevant member state has implemented the relevant provision of the 2010 PD Amending Directive, 150 natural or legal persons (other than qualified investors as defined in the Prospectus Directive), as permitted under the Prospectus Directive, subject to obtaining the prior consent of the relevant Dealer or Dealers nominated by us for any such offer; or

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in any other circumstances falling within Article 3(2) of the Prospectus Directive, provided that no such offer of shares shall require us or any underwriter to publish a prospectus pursuant to Article 3 of the Prospectus Directive.

For purposes of this provision, the expression an offer of securities to the public in any relevant member state means the communication in any form and by any means of sufficient information on the terms of the offer and the shares to be offered so as to enable an investor to decide to purchase or subscribe for the shares, as the expression may be varied in that member state by any measure implementing the Prospectus Directive in that member state, and the expression Prospectus Directive means Directive 2003/71/EC (and amendments thereto, including the 2010 PD Amending Directive, to the extent implemented in the relevant member state) and includes any relevant implementing measure in the relevant member state. The expression 2010 PD Amending Directive means Directive 2010/73/EU.

The sellers of the shares have not authorized and do not authorize the making of any offer of shares through any financial intermediary on their behalf, other than offers made by the underwriters with a view to the final placement of the shares as contemplated in this prospectus supplement. Accordingly, no purchaser of the shares, other than the underwriters, is authorized to make any further offer of the shares on behalf of the sellers or the underwriters.

Notice to Prospective Investors in the United Kingdom

This prospectus supplement is only being distributed to, and is only directed at, persons in the United Kingdom that are qualified investors within the meaning of Article 2(1)(e) of the Prospectus Directive that are also (1) investment professionals falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, or the Order, or (2) high net worth entities, and other persons to whom it may lawfully be communicated, falling within Article 49(2)(a) to (d) of the Order (each such person being referred to as a relevant person). This prospectus supplement and its contents are confidential and should not be distributed, published or reproduced (in whole or in part) or disclosed by recipients to any other persons in the United Kingdom. Any person in the United Kingdom that is not a relevant person should not act or rely on this document or any of its contents.

Notice to Prospective Investors in France

Neither this prospectus supplement nor any other offering material relating to the shares described in this prospectus supplement has been submitted to the clearance procedures of the Autorité des Marchés Financiers or of the competent authority of another member state of the European Economic Area and notified to the Autorité des Marchés Financiers. The shares have not been offered or sold and will not be offered or sold, directly or indirectly, to the public in France. Neither this prospectus supplement nor any other offering material relating to the shares has been or will be:

released, issued, distributed or caused to be released, issued or distributed to the public in France; or

used in connection with any offer for subscription or sale of the shares to the public in France. Such offers, sales and distributions will be made in France only:

to qualified investors (investisseurs qualifiés) or to a restricted circle of investors (cercle restreint d'investisseurs), in each case investing for their own account, all as defined in, and in accordance with

articles L.411-2, D.411-1, D.411-2, D.734-1, D.744-1, D.754-1 and D.764-1 of the French Code monétaire et financier;

to investment services providers authorized to engage in portfolio management on behalf of third parties; or

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in a transaction that, in accordance with article L.411-2-II-1^o-or-2^o-or 3^o of the French Code monétaire et financier and article 211-2 of the General Regulations (Règlement Général) of the Autorité des Marchés Financiers, does not constitute a public offer (appel public à l'épargne).

The shares may be resold directly or indirectly, only in compliance with articles L.411-1, L.411-2, L.412-1 and L.621-8 through L.621-8-3 of the French *Code monétaire et financier*.

Notice to Prospective Investors in Hong Kong

The shares may not be offered or sold in Hong Kong by means of any document other than (1) in circumstances which do not constitute an offer to the public within the meaning of the Companies Ordinance (Cap. 32, Laws of Hong Kong), (2) to professional investors within the meaning of the Securities and Futures Ordinance (Cap. 571, Laws of Hong Kong) and any rules made thereunder, or (3) in other circumstances which do not result in the document being a prospectus within the meaning of the Companies Ordinance (Cap. 32, Laws of Hong Kong) and no advertisement, invitation or document relating to the shares may be issued or may be in the possession of any person for the purpose of issue (in each case whether in Hong Kong or elsewhere), which is directed at, or the contents of which are likely to be accessed or read by, the public in Hong Kong (except if permitted to do so under the laws of Hong Kong) other than with respect to shares which are or are intended to be disposed of only to persons outside Hong Kong or only to professional investors within the meaning of the Securities and Futures Ordinance (Cap. 571, Laws of Hong Kong) and any rules made thereunder.

Notice to Prospective Investors in Japan

The shares offered in this prospectus supplement have not been and will not be registered under the Financial Instruments and Exchange Law of Japan. The shares have not been offered or sold and will not be offered or sold, directly or indirectly, in Japan or to or for the account of any resident of Japan (including any corporation or other entity organized under the laws of Japan), except (1) pursuant to an exemption from the registration requirements of the Financial Instruments and Exchange Law and (2) in compliance with any other applicable requirements of Japanese law.

Notice to Prospective Investors in Singapore

This prospectus supplement has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus supplement and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the shares may not be circulated or distributed, nor may the shares be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (1) to an institutional investor under Section 274 of the Securities and Futures Act, Chapter 289 of Singapore, or the SFA, (2) to a relevant person pursuant to Section 275(1), or any person pursuant to Section 275(1A), and in accordance with the conditions specified in Section 275 of the SFA, or (3) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA, in each case subject to compliance with conditions set forth in the SFA.

Where the shares are subscribed or purchased under Section 275 of the SFA by a relevant person which is:

a corporation (which is not an accredited investor (as defined in Section 4A of the SFA)) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or

a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary of the trust is an individual who is an accredited investor, shares, debentures and units of shares and debentures of that corporation or the beneficiaries' rights and interest (howsoever

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described) in that trust shall not be transferred within six months after that corporation or that trust has acquired the shares pursuant to an offer made under Section 275 of the SFA except:

to an institutional investor (for corporations, under Section 274 of the SFA) or to a relevant person defined in Section 275(2) of the SFA, or to any person pursuant to an offer that is made on terms that such shares, debentures and units of shares and debentures of that corporation or such rights and interest in that trust are acquired at a consideration of not less than S\$200,000 (or its equivalent in a foreign currency) for each transaction, whether such amount is to be paid for in cash or by exchange of securities or other assets, and further for corporations, in accordance with the conditions specified in Section 275 of the SFA;

where no consideration is or will be given for the transfer; or

where the transfer is by operation of law.

Notice to Prospective Investors in Australia

No prospectus or other disclosure document (as defined in the Corporations Act 2001 (Cth) of Australia, or the Corporations Act) in relation to the common stock has been or will be lodged with the Australian Securities & Investments Commission, or ASIC. This document has not been lodged with ASIC and is only directed to certain categories of exempt persons. Accordingly, if you receive this document in Australia:

you confirm and warrant that you are either:

a sophisticated investor under section 708(8)(a) or (b) of the Corporations Act;

a sophisticated investor under section 708(8)(c) or (d) of the Corporations Act and that you have provided an accountant's certificate to us which complies with the requirements of section 708(8)(c)(i) or (ii) of the Corporations Act and related regulations before the offer has been made;

a person associated with the company under section 708(12) of the Corporations Act; or

a professional investor within the meaning of section 708(11)(a) or (b) of the Corporations Act, and to the extent that you are unable to confirm or warrant that you are an exempt sophisticated investor, associated person or professional investor under the Corporations Act any offer made to you under this document is void and incapable of acceptance; and

you warrant and agree that you will not offer any of the common stock for resale in Australia within 12 months of that common stock being issued unless any such resale offer is exempt from the requirement to issue a disclosure document under section 708 of the Corporations Act.

Notice to Prospective Investors in Canada

The shares may be sold only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 Prospectus Exemptions or subsection 73.3(1) of the Securities Act (Ontario), and are permitted clients, as defined in National Instrument 31-103 Registration Requirements, Exemptions and Ongoing Registrant Obligations. Any resale of the shares must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus supplement and accompanying prospectus (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser's province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser's province or territory for particulars of these rights or consult with a legal advisor.

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Pursuant to section 3A.3 of National Instrument 33-105 Underwriting Conflicts (NI 33-105), the underwriter is not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

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LEGAL MATTERS

The validity of the common stock offered by us in this prospectus supplement and the accompanying prospectus will be passed upon for us by Cooley LLP, San Diego, California. Certain legal matters in connection with the offering will be passed upon for the underwriters by Latham & Watkins 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, 2016, as set forth in their report, which is incorporated by reference into this prospectus supplement and the accompanying prospectus. 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 website at www.sec.gov or on our website at www.regulusrx.com. Information included on our website is not part of this prospectus supplement or the accompanying prospectus.

This prospectus supplement and the accompanying prospectus are part of an effective registration statement that we filed with the SEC. The registration statement contains more information than this prospectus supplement and the accompanying prospectus regarding us and our securities, including exhibits and schedules. You can obtain a copy of the registration statement from the SEC at their address listed above or from the SEC's website.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to incorporate by reference the 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. Information that we incorporate by reference is considered part of this prospectus supplement and the accompanying prospectus.

We incorporate by reference the documents listed below and any future filings made with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of this prospectus supplement until the termination of the offering of the shares covered by this prospectus supplement (other than current reports furnished under Item 2.02 or Item 7.01 of Form 8-K and exhibits filed on such form that are related to such items):

our Annual Report on Form 10-K for the year ended December 31, 2016, filed with the SEC on March 3, 2017;

our Quarterly Report on Form 10-Q for the quarter ended March 31, 2017, filed with the SEC on May 5, 2017;

our Current Reports on Form 8-K filed with the SEC on January 27, 2017, May 4, 2017, May 26, 2017, June 2, 2017, June 12, 2017 and July 19, 2017;

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the information specifically incorporated by reference into our Annual Report on Form 10-K for the year ended December 31, 2016 from our definitive proxy statement on Schedule 14A filed with the SEC on April 28, 2017; and

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 10614 Sciences Center Drive, San Diego, California 92121, Attention: Secretary, or telephoning us at (858) 202-6300.

In accordance with Rule 412 of the Securities Act, any statement contained in a document incorporated by reference herein shall be deemed modified or superseded to the extent that a statement contained herein or in any other subsequently filed document which also is or is deemed to be incorporated by reference herein modifies or supersedes such statement.

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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.

Our common stock is listed on The NASDAQ Global Market under the trading symbol "RGLS". The last reported sale price of our common stock on The NASDAQ Global Market on April 28, 2016 was \$6.16 per share. You are encouraged to obtain current market quotations for shares of our common stock.

Our principal executive offices are located at 3545 John Hopkins Ct., Suite 210, San Diego, California 92121, and our telephone number at that address is (858) 202-6300.

INVESTING IN OUR COMMON STOCK INVOLVES A HIGH DEGREE OF RISK. YOU SHOULD REVIEW CAREFULLY THE RISKS AND UNCERTAINTIES REFERENCED UNDER THE HEADING RISK FACTORS ON PAGE 6 OF THIS PROSPECTUS AS WELL AS THOSE CONTAINED IN ANY APPLICABLE PROSPECTUS SUPPLEMENT AND ANY RELATED FREE WRITING PROSPECTUS, AND UNDER SIMILAR HEADINGS IN THE OTHER DOCUMENTS THAT ARE INCORPORATED BY REFERENCE INTO THIS PROSPECTUS.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

This prospectus may not be used to consummate sales of securities unless, to the extent required by applicable law, it is accompanied by a prospectus supplement.

Prospectus dated May 2, 2016

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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*SM, a division focused on identifying *microRNAs* as biomarkers of human disease to support our therapeutic pipeline, collaborators and strategic partners. Regulus *microMarkers*SM 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. 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, may, 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*SM 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;

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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. 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.

