

Regulus Therapeutics Inc.
Form 424B5
October 27, 2014
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Filed Pursuant to Rule 424(b)(5)
Registration No. 333-194293

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.

SUBJECT TO COMPLETION, DATED OCTOBER 27, 2014

PRELIMINARY PROSPECTUS SUPPLEMENT

(To Prospectus dated April 16, 2014)

\$80,000,000

Common Stock

We are offering \$70,000,000 of shares of our common stock and the selling stockholder identified in this prospectus supplement is offering \$10,000,000 of shares of our common stock. We will not receive any proceeds from the sale of shares by the selling stockholder. Our common stock is listed on The NASDAQ Global Market under the symbol RGLS. On October 24, 2014, the last sale price of our common stock as reported on The NASDAQ Global Market was \$17.33 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-7 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	\$	\$

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Proceeds, before expenses, to selling stockholder \$ \$

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

The underwriters have been granted an option to purchase up to an additional \$6,000,000 of shares from us and up to an additional \$6,000,000 of shares from the selling stockholder at the public offering price, less the underwriting discount, for a period of 30 days following the date of this prospectus supplement. If the underwriters exercise the option in full, the total underwriting discounts and commissions payable by us will be \$, the total underwriting discounts and commissions payable by the selling stockholder will be \$, the total proceeds to us, before expenses, will be \$ and the total proceeds to the selling stockholder, 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 , 2014.

Joint Book-Running Managers

Deutsche Bank Securities

BMO Capital Markets

Co-Managers

Needham & Company

**WedBush PacGrow
Life Sciences**

FBR

Prospectus Supplement dated October , 2014

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We and the selling stockholder 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 and the selling stockholder 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

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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 April 16, 2014, 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-7 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 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 Isis Pharmaceuticals, Inc., or Isis, 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. *microRNAs* are recently discovered, 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. 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, key opinion leaders and disciplined drug discovery and development processes. 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. We use these anti-miRs to modulate *microRNAs* and by doing so return diseased cells to their healthy state. We are pursuing several *microRNA* targets and are focusing our proprietary efforts in oncology and orphan diseases. 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, biologics and monoclonal antibodies. Additionally, 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, including small molecules and monoclonal antibodies. In January 2014, we expanded our biomarkers efforts and established *microMarkers*, a division focused on identifying *microRNAs* as biomarkers of human disease, which is designed to support our therapeutic pipeline, collaborators and strategic partners. In August 2014, we entered into a new research collaboration with Biogen Idec to identify *microRNA* biomarkers for multiple sclerosis, and we have also entered into an arrangement with another leading, commercial-stage pharmaceutical company to explore *microRNAs* as biomarkers for specific patient populations.

We are developing RG-101, our wholly-owned GalNAc-conjugated anti-miR targeting *microRNA*-122 for the treatment of chronic hepatitis C virus infection, or HCV, and RG-012, an anti-miR targeting *microRNA*-21 for the treatment of Alport syndrome, a life-threatening kidney disease driven by genetic mutations with no approved therapy. In addition to these programs, we are also advancing several programs toward clinical development in oncology, fibrosis and metabolic diseases, both independently and with our strategic alliance partners AstraZeneca AB and Sanofi.

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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 \$107.8 million upon achievement of preclinical and investigational new drug application milestones, up to \$138.0 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.

Recent Developments

In September 2014, we announced the initiation of our ATHENA natural history of disease study in patients with Alport syndrome. The ATHENA study is designed to characterize the natural decline of renal function markers in Alport syndrome patients over time. Over the course of two years, we aim to enroll up to 120 Alport syndrome patients who are 16 years and older with a glomerular filtration rate between 30 to 75 milliliters per minute at planned clinical sites in the United States, Australia, Canada and Europe. We believe the data collected from the ATHENA study will provide much needed information about the changes in renal function over time in Alport syndrome patients, which will inform future clinical development plans for RG-012.

In October 2014, we announced interim results from our ongoing clinical study evaluating RG-101 that demonstrate human proof-of-concept with a *microRNA* therapeutic. Interim results from the ongoing clinical study demonstrate that treatment with a single subcutaneous dose of 2 mg/kg of RG-101 as monotherapy resulted in significant and sustained reductions in HCV RNA in a varied group of patients, including difficult to treat genotypes and patients who experienced viral relapse after a prior interferon, or IFN, containing regimen. Additionally, RG-101 was safe and well tolerated and has demonstrated a very favorable pharmacokinetic profile to date, which may allow for combination with oral direct-acting antiviral agents to treat HCV.

We plan to complete our ongoing clinical study of RG-101 in the first quarter of 2015. Additionally, we intend to file an Investigational New Drug application with the U.S. Food and Drug Administration and submit safety, tolerability, pharmacokinetics and pharmacodynamics data sets for publication during the first quarter of 2015. In the second quarter of 2015, we expect to report our full HCV patient data set regarding RG-101 at a medical meeting and also plan to initiate a Phase 2 combination study of RG-101 in HCV patients.

Preliminary Cash Position as of September 30, 2014

Our cash, cash equivalents and short-term investments were approximately \$94.1 million as of September 30, 2014. 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 September 30, 2014. Our condensed financial statements as of and for the quarter ended September 30, 2014 will not be available until after this offering is complete, and consequently will not be available to you prior to investing in this offering.

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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 supplement or the accompanying prospectus, and the inclusion of our website address in this prospectus supplement is an inactive textual reference only.

We use *Regulus Therapeutics* as a trademark in the United States and other countries. We have registered this trademark 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 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 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, (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	\$70,000,000 of shares
Common stock offered by selling stockholder	\$10,000,000 of shares
Common stock to be outstanding immediately after this offering	47,423,101 shares (or 47,769,322 shares if the underwriters exercise in full their option to purchase additional shares)
Option to purchase additional shares	The underwriters have been granted an option to purchase up to an aggregate of \$6,000,000 of additional shares of our common stock from us and \$6,000,000 of additional shares from the selling stockholder. 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 preclinical and clinical development of our clinical candidates, RG-101 and RG-012, and our other initial <i>micro</i> RNA development candidates, for the identification and validation of additional <i>micro</i> RNA 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>micro</i> RNA businesses, technologies, products or assets. However, we have no current commitments or obligations to do so. See <i>Use of Proceeds</i> on page S-10 of this prospectus supplement. We will not receive any proceeds from the sale of shares of common stock by the selling stockholder.
Risk factors	Investing in our common stock involves significant risks. See <i>Risk Factors</i> beginning on page S-7 of this prospectus supplement.
NASDAQ Global Market symbol	Our common stock is listed on The NASDAQ Global Market under the symbol <i>RGLS</i> . The number of shares of our common stock to be outstanding immediately after this offering is based on 43,383,863 shares outstanding as of June 30, 2014 and assumes the sale by us of \$70,000,000 of shares of common stock at \$17.33 per share, the last reported sale price of our common stock on The NASDAQ Global Market on October 24, 2014. The number of shares excludes, as of June 30, 2014:

6,387,153 shares of common stock issuable upon the exercise of outstanding stock options under our equity incentive plans, with a weighted average exercise price of \$4.45 per share;

1,319,855 shares of common stock available for future grants under our 2012 equity incentive plan;

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858,625 shares of common stock available for issuance under our employee stock purchase plan; and

1,437,053 shares of common stock issuable upon conversion of a convertible note at a conversion price of \$4.00 per share.
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. In assessing the risks described below, you should also refer to the information contained in our Quarterly Report on Form 10-Q for the quarter ended June 30, 2014 and other documents which are 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 an assumed public offering price of \$17.33 per share (the last reported sale price for our common stock on The NASDAQ Global Market on October 24, 2014) and our net tangible book value as of June 30, 2014, if you purchase shares of common stock in this offering, you will suffer immediate and substantial dilution of \$14.25 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 as well as a convertible note outstanding. To the extent these securities have been or may be exercised or converted 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 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 future 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;

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;

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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;

our use of the proceeds from our prior public offerings and this offering; and

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

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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 \$65.3 million (or \$70.9 million if the underwriters' option to purchase additional shares from us is exercised in full), after payment of estimated underwriting discounts and commissions and estimated offering expenses payable by us. We will not receive any proceeds from the sale of shares of common stock offered by the selling stockholder.

We intend to use the net proceeds from the shares offered by us in this offering for general corporate purposes, including preclinical and clinical development of our clinical candidates, RG-101 and RG-012, and our other initial *microRNA* development candidates, 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.

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DILUTION

Our net tangible book value as of June 30, 2014 was approximately \$81.0 million, or \$1.87 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 June 30, 2014. 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 \$70,000,000 of shares of our common stock by us in this offering at the assumed public offering price of \$17.33 per share (the last reported sale price for our common stock on The NASDAQ Global Market on October 24, 2014) 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 June 30, 2014 would have been approximately \$146.3 million, or \$3.08 per share. This represents an immediate increase in net tangible book value of \$1.21 per share to existing stockholders and immediate dilution in value of \$14.25 per share to investors purchasing common stock in this offering.

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

Assumed public offering price per share	\$ 17.33
Net tangible book value per share as of June 30, 2014	\$ 1.87
Increase in net tangible book value per share attributable to new investors purchasing our common stock in this offering	1.21
As adjusted net tangible book value per share on June 30, 2014, after giving effect to this offering	3.08
Dilution per share to new investors purchasing our common stock in this offering	\$ 14.25

If the underwriters exercise in full their option to purchase up to \$6,000,000 of additional shares of common stock from us in this offering at the assumed public offering price of \$17.33 per share, the as adjusted net tangible book value after this offering would have been \$3.18 per share, representing an increase in net tangible book value of \$1.31 per share to existing stockholders and immediate dilution in value of \$14.15 per share to investors purchasing common stock in this offering at the public offering price.

The above discussion and table are based on 43,383,863 shares outstanding as of June 30, 2014, and exclude as of that date:

6,387,153 shares of common stock issuable upon the exercise of outstanding stock options under our equity incentive plans, with a weighted average exercise price of \$4.45 per share;

1,319,855 shares of common stock available for future grants under our 2012 equity incentive plan;

858,625 shares of common stock available for issuance under our employee stock purchase plan; and

1,437,053 shares of common stock issuable upon conversion of a convertible note at a conversion price of \$4.00 per share.

To the extent that stock options or our outstanding convertible note as of June 30, 2014 have been or may be exercised or converted or other securities issued, investors purchasing our common stock in this offering may experience further dilution. In addition, we may choose to

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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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The following table sets forth information as of October 24, 2014 regarding beneficial ownership of our common stock by the selling stockholder that is offering shares of our common stock pursuant to this prospectus supplement. When we refer to the selling stockholder in this prospectus supplement, we mean the entity listed in the table below.

This table below was prepared based on information supplied to us by the selling stockholder and reflects holdings as of October 24, 2014.

The number of shares and percentage ownership information after the offering is based on 43,689,880 shares of our common stock outstanding as of October 24, 2014 and the sale by us of \$70,000,000 of shares in this offering and the sale of \$10,000,000 of shares by the selling stockholder in this offering, in each case at the assumed public offering price of \$17.33 per share (the last reported sale price for our common stock on The NASDAQ Global Market on October 24, 2014).

Beneficial ownership is determined in accordance with Section 13(d) of the Exchange Act and the rules and regulations thereunder.

Name and Address	Shares of Common Stock Beneficially Owned Before Offering	Number of Shares Being Offered	Shares of Common Stock Beneficially Owned Following the Offering	
	Number		% of Class	
Isis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, CA 92010	6,820,716(1)	577,034	6,243,682	13.1%

(1) Includes 25,000 shares that Stanley T. Crooke, M.D., Ph.D., one of our former directors, has the right to acquire from us within 60 days of October 24, 2014 pursuant to the exercise of stock options.

Until November 5, 2012, Isis had two representatives on our board of directors. As of the date of this prospectus supplement, Isis continues to have one representative on our board of directors. In addition, we have formed strategic alliances with Isis pursuant to a license and collaboration agreement dated September 2007 with Isis and Alnylam Pharmaceuticals, Inc., which we subsequently amended, restated and superseded in January 2009, and further amended in June 2010, October 2011 and August 2013. This agreement, as amended, is described in our Annual Report for the year ended December 31, 2013, filed with the SEC on February 28, 2014 (File No. 001-35670), which description is incorporated by reference herein.

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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 U.S. 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 U.S. 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, 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, and U.S. expatriates and certain former citizens or long-term residents of the United States.

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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 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](#).

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 that is eligible for a reduced rate of U.S. withholding tax under an income tax treaty may obtain a refund or credit of any excess amounts withheld by timely filing an appropriate claim for refund with the IRS. 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.

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 U.S. 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 U.S. 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 U.S. 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 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 U.S. 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

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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 the holder is a U.S. 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 the holder is a U.S. 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

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stock on or after January 1, 2017. Under certain circumstances, a non-U.S. holder might be eligible for refunds or credits of such taxes. 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.

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UNDERWRITING

We have entered into an underwriting agreement with Deutsche Bank Securities Inc. and BMO Capital Markets Corp., as representatives of the underwriters named below, with respect to the common stock subject to this offering. Subject to certain conditions, we have agreed to sell to the underwriters, and the underwriters have severally agreed to purchase from us and the selling stockholder, at the public offering price less the underwriting discounts and commissions set forth on the cover page of this prospectus supplement, the number of shares of common stock listed next to each underwriter's name below. Our common stock is listed on the Nasdaq Global Market under the symbol RGLS.

Underwriters	Number of Shares
Deutsche Bank Securities Inc.	
BMO Capital Markets Corp.	
Needham & Company, LLC	
Wedbush Securities Inc.	
FBR Capital Markets & Co.	

Total

The underwriting agreement provides that the obligations of the several underwriters to purchase the shares of common stock offered hereby are subject to certain conditions precedent and that the underwriters will purchase all of the shares of common stock offered by this prospectus supplement, other than those covered by the option to purchase additional shares described below, if any of these shares are purchased. The underwriting agreement also provides that if an underwriter defaults, the purchase commitments of non-defaulting underwriters may also be increased or this offering may be terminated.

We and the selling stockholder have agreed to indemnify the underwriters against some specified types of liabilities, including liabilities under the Securities Act, and to contribute to payments the underwriters may be required to make in respect of any of these 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 officer's 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

We have been advised by the representatives of the underwriters that the underwriters propose to offer the shares of common stock to the public at the public offering price set forth on the cover of this prospectus supplement and to dealers at a price that represents a concession not in excess of \$ _____ per share under the public offering price. The underwriters may allow, and these dealers may re-allow, a concession of not more than \$ _____ per share to other dealers.

The underwriting discounts and commissions per share are equal to the public offering price per share of common stock less the amount paid by the underwriters to us per share of common stock. The underwriting discounts and commissions are _____ % of the public offering

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price. We have agreed to pay the underwriters the following discounts and commissions, assuming either no exercise or full exercise by the underwriters of the underwriters option to purchase additional shares:

	Per Share	Without Exercise of Option to Purchase Additional Shares	Total Fees With Full Exercise of Option to Purchase Additional Shares
Discounts and commissions paid by us	\$	\$	\$
Discounts and commissions paid by the selling stockholder	\$	\$	\$

We estimate that our share of the total expenses of this offering, excluding underwriting discounts and commissions, will be approximately \$496,000. We have also agreed with the underwriters to pay all fees and expenses related to the review and qualification of this offering by the Financial Industry Regulatory Authority, Inc. (FINRA) in an aggregate amount not to exceed \$10,000.

The representatives of the underwriters have advised us that the underwriters do not intend to confirm sales to any account over which they exercise discretionary authority.

Option to Purchase Additional Shares

We and the selling stockholder have granted to the underwriters an option, exercisable not later than 30 days after the date of this prospectus supplement, to purchase up to \$12,000,000 of additional shares of common stock at the public offering price less the underwriting discounts and commissions set forth on the cover page of this prospectus supplement. To the extent that the underwriters exercise this option, each of the underwriters will become obligated, subject to conditions, to purchase approximately the same percentage of these additional shares of common stock as the number of shares of common stock to be purchased by it in the above table bears to the total number of shares of common stock offered by this prospectus supplement. We will be obligated, pursuant to the option, to sell these additional shares of common stock to the underwriters to the extent the option is exercised. If any additional shares of common stock are purchased, the underwriters will offer the additional shares on the same terms as those on which the initial shares referred to in the above table are being offered.

No Sales of Similar Securities

We and all of our directors and officers, the selling stockholder and a certain of our other stockholders have agreed that, subject to certain exceptions, without the prior written consent of Deutsche Bank Securities Inc. and BMO Capital Markets Corp. on behalf of the underwriters, we and they will not, during the period ending 90 days after the date of this prospectus supplement:

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.

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There are no agreements between the representatives and any party to these lock-up agreements releasing such party from the lock-up agreements prior to the expiration of the 90-day period.

Price Stabilization, Short Positions and Penalty Bids

In connection with this offering, the underwriters may purchase and sell shares of our common stock in the open market. These transactions may include short sales, purchases 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 this offering. Covered short sales are sales made in an amount not greater than the underwriters' option to purchase additional shares of common stock from us and the selling stockholder in this offering. The underwriters may close out any covered short position by either exercising their option to purchase additional shares 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 additional shares of common stock pursuant to the option granted to them. Naked short sales are any 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 underwriters are concerned that there may be downward pressure on the price of the shares in the open market prior to the completion of this offering. Stabilizing transactions consist of various bids for or purchases of our common stock made by the underwriters in the open market prior to the completion of this offering.

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

Purchases to cover a short position and stabilizing transactions may have the effect of preventing or slowing a decline in the market price of our common stock. Additionally, these purchases, along with the imposition of the penalty bid, may stabilize, maintain or otherwise affect 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. These transactions may be effected on the Nasdaq Global Market, in the over-the-counter market or otherwise.

Electronic Offer, Sale and Distribution of Shares

This prospectus supplement and the accompanying prospectus may be made available in electronic format on the Internet sites or through other online services maintained by the underwriters participating in the offering or by their affiliates. In those cases, prospective investors may view offering terms online and prospective investors may be allowed to place orders online. Other than the prospectus supplement and the accompanying prospectus in electronic format, the information on the underwriters' or our website and any information contained in any other website maintained by the underwriters or by us is not part of the prospectus supplement, the accompanying prospectus or the registration statement of which this prospectus supplement and the accompanying prospectus form a part, has not been approved and/or endorsed by us or the underwriters in their capacity as underwriters and should not be relied upon by investors.

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Other Relationships

Some of the underwriters and their affiliates have engaged in, and may in the future engage in, investment banking and other commercial dealings in the ordinary course of business with us, the selling stockholder or our or the selling stockholder's respective affiliates. They have received, or may in the future receive, customary fees and commissions for these transactions.

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.

Selling Restrictions

Notice to Prospective Investors in the European Economic Area

In relation to each Member State of the European Economic Area which has implemented the Prospectus Directive (each, a Relevant Member State), each underwriter has represented and agreed that with effect from and including the date on which the Prospectus Directive is implemented in that Relevant Member State (the Relevant Implementation Date) it has not made and will not make an offer of shares to the public in that Relevant Member State prior to the publication of a prospectus in relation to the shares which has been approved by the competent authority in that Relevant Member State or, where appropriate, approved in another Relevant Member State and notified to the competent authority in that Relevant Member State, all in accordance with the Prospectus Directive, except that it may, with effect from and including the Relevant Implementation Date, make an offer of shares to the public in that Relevant Member State at any time:

- (a) to any legal entity which is a qualified investor as defined in the Prospectus Directive;
- (b) 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) subject to obtaining the prior consent of the representatives for any such offer; or
- (c) in any other circumstances which do not require the publication by us of a prospectus pursuant to Article 3 of the Prospectus Directive.

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

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Notice to Prospective Investors in the United Kingdom

This prospectus supplement and any other material in relation to the shares described herein 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 Prospective Directive ("qualified investors") that also (i) have professional experience in matters relating to investments falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, as amended, or the Order, (ii) who fall within Article 49(2)(a) to (d) of the Order or (iii) to whom it may otherwise lawfully be communicated (all such persons together being referred to as "relevant persons"). The shares are only available to, and any invitation, offer or agreement to purchase or otherwise acquire such shares will be engaged in only with, relevant persons. 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 person in the United Kingdom. Any person in the United Kingdom that is not a relevant person should not act or rely on this prospectus supplement or any of its contents.

Notice to Prospective Investors in Switzerland

The shares may not be publicly offered in Switzerland and will not be listed on the SIX Swiss Exchange (the "SIX") or on any other stock exchange or regulated trading facility in Switzerland. This document has been prepared without regard to the disclosure standards for issuance prospectuses under art. 652a or art. 1156 of the Swiss Code of Obligations or the disclosure standards for listing prospectuses under art. 27 ff. of the SIX Listing Rules or the listing rules of any other stock exchange or regulated trading facility in Switzerland. Neither this document nor any other offering or marketing material relating to the shares or the offering may be publicly distributed or otherwise made publicly available in Switzerland.

Neither this prospectus supplement nor any other offering or marketing material relating to the offering, the issuer, the shares have been or will be filed with or approved by any Swiss regulatory authority. In particular, this prospectus supplement will not be filed with, and the offer of shares will not be supervised by, the Swiss Financial Market Supervisory Authority FINMA (the "FINMA"), and the offer of shares has not been and will not be authorized under the Swiss Federal Act on Collective Investment Schemes (the "CISA"). The investor protection afforded to acquirers of interests in collective investment schemes under the CISA does not extend to acquirers of shares.

Notice to Prospective Investors in the Dubai International Financial Centre

This prospectus supplement relates to an Exempt Offer in accordance with the Offered Securities Rules of the Dubai Financial Services Authority (the "DFSA"). This prospectus supplement is intended for distribution only to persons of a type specified in the Offered Securities Rules of the DFSA. It must not be delivered to, or relied on by, any other person. The DFSA has no responsibility for reviewing or verifying any documents in connection with Exempt Offers. The DFSA has not approved this prospectus supplement nor taken steps to verify the information set forth herein and has no responsibility for this prospectus supplement. The shares to which this prospectus supplement relates may be illiquid and/or subject to restrictions on their resale. Prospective purchasers of the shares offered should conduct their own due diligence on the shares. If you do not understand the contents of this prospectus supplement you should consult an authorized financial advisor.

Notice to Prospective Investors in Hong Kong

The shares may not be offered or sold by means of any document other than (i) in circumstances which do not constitute an offer to the public within the meaning of the

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Companies Ordinance (Cap. 32, Laws of Hong Kong), or (ii) to professional investors within the meaning of the Securities and Futures Ordinance (Cap. 571, Laws of Hong Kong) and any rules made thereunder, or (iii) 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 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 (i) to an institutional investor under Section 274 of the Securities and Futures Act, Chapter 289 of Singapore (the SFA), (ii) to a relevant person, or any person pursuant to Section 275(1A), and in accordance with the conditions, specified in Section 275 of the SFA or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA.

Where the shares are subscribed or purchased under Section 275 by a relevant person which is: (a) a corporation (which is not an accredited investor) 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 (b) a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary is an accredited investor, shares, debentures and units of shares and debentures of that corporation or the beneficiaries' rights and interest in that trust shall not be transferable for six months after that corporation or that trust has acquired the shares under Section 275 except: (1) to an institutional investor under Section 274 of the SFA or to a relevant person, or any person pursuant to Section 275(1A), and in accordance with the conditions, specified in Section 275 of the SFA; (2) where no consideration is given for the transfer; or (3) by operation of law.

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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, 2013, 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, 2013, as filed with the SEC on February 28, 2014;

the information specifically incorporated by reference into our Annual Report on Form 10-K for the year ended December 31, 2013 from our definitive proxy statement on Schedule 14A filed with the SEC on April 11, 2014;

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our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2014 and June 30, 2014, filed with the SEC on May 9, 2014 and August 7, 2014, respectively;

our Current Reports on Form 8-K filed with the SEC on February 5, 2014, March 11, 2014, May 23, 2014, September 19, 2014 and October 22, 2014; 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 3545 John Hopkins Court, Suite 210, 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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\$100,000,000
Common Stock
Warrants
8,600,000 Shares of Common Stock
Offered by Selling Stockholders

We may from time to time offer and sell up to \$100,000,000 aggregate dollar amount of common stock and warrants to purchase common stock in one or more offerings. In addition, the selling stockholders identified in this prospectus may sell, from time to time, up to 8,600,000 shares of our common stock. We will not receive any proceeds from sales by the selling stockholders. This prospectus provides you with a general description of the securities.

We will provide the specific terms of these offerings and securities in one or more supplements 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. Any prospectus supplement and any related free writing prospectus may also add, update or change information contained in this prospectus. You should carefully read this prospectus, any applicable prospectus supplement and any related free writing prospectus, as well as any documents incorporated by reference, before buying any of the securities being offered.

The securities may be sold directly by us to investors, through agents designated from time to time or to or through underwriters or dealers, on a continuous or delayed basis. For additional information on the methods of sale, you should refer to the section entitled "Plan of Distribution" in this prospectus. If any agents or underwriters are involved in the sale of any securities with respect to which this prospectus is being delivered, the names of such agents or underwriters and any applicable fees, commissions, discounts and over-allotment options will 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 11, 2014 was \$7.39 per share. Any applicable prospectus supplement will contain information, where applicable, as to other listings, if any, on the Nasdaq Global Market or other securities exchange of the securities covered by the applicable prospectus supplement.

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 SECURITIES INVOLVES A HIGH DEGREE OF RISK. YOU SHOULD REVIEW CAREFULLY THE RISKS AND UNCERTAINTIES REFERENCED UNDER THE HEADING "RISK FACTORS" ON PAGE 4 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 April 16, 2014

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You should rely only on the information contained or incorporated by reference in this prospectus, any accompanying prospectus supplement or any free writing prospectus we may authorize to be delivered to you. We have not authorized anyone to provide you with different information. If anyone provides you with different or inconsistent information, you should not rely on it. You should assume that the information appearing in this prospectus, any prospectus supplement and the documents incorporated by reference herein and therein are accurate only as of their respective dates. Our business, financial condition, results of operations and prospects may have changed since those dates. Neither this prospectus nor any accompanying prospectus supplement shall constitute an offer or solicitation by anyone in any jurisdiction in which such offer or solicitation is not authorized or in which the person making such offer or solicitation is not qualified to do so or to anyone to whom it is unlawful to make such offer or solicitation.

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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 a shelf registration process. Under this shelf registration process, we may from time to time sell common stock and warrants, or any combination of these securities, in one or more offerings up to a total dollar amount of \$100,000,000. In addition, under this shelf process, the selling stockholders may sell from time to time up to 8,600,000 shares of our common stock. This prospectus provides you with a general description of the securities we and/or the selling stockholders may offer. Each time we and/or the selling stockholders offer securities under this prospectus, we will provide a prospectus supplement that will contain more specific information about the terms of that offering to the extent required by applicable law. We may also authorize one or more free writing prospectuses to be provided to you that may contain material information relating to these offerings. 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 securities 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 securities 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 stockholders 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 securities 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 that 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

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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 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 Additional 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 Isis Pharmaceuticals, Inc., or Isis, 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. *microRNAs* are recently discovered, 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. 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, key opinion leaders and disciplined drug discovery and development processes. 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. We use these anti-miRs to modulate *microRNAs* and by doing so return diseased cells to their healthy state. We are pursuing several *microRNA* targets and are focusing our proprietary efforts in oncology and orphan diseases. 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, biologics and monoclonal antibodies. Additionally, 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, including small molecules and monoclonal antibodies. In January 2014, we expanded our biomarkers efforts and established *microMarkers*, a research and development division focused on identifying *microRNAs* as biomarkers of human disease, which is designed to support our therapeutic pipeline, collaborators and strategic partners.

We are currently optimizing anti-miRs in several distinct programs, both independently and with our strategic alliance partners, AstraZeneca AB, or AstraZeneca, GlaxoSmithKline plc and Sanofi. We also have a collaboration agreement with Biogen Idec MA Inc. to evaluate the potential use of *microRNA* signatures as a biomarker for human patients with multiple sclerosis. Under these strategic alliances, we are eligible to receive up to approximately \$1.5 billion in milestone payments upon successful commercialization of *microRNA* therapeutics for the programs contemplated by our agreements. These payments include up to \$128.0 million upon achievement of preclinical and investigational new drug application milestones, up to \$254.0 million upon achievement of clinical development milestones, up to \$380.0 million upon achievement of regulatory milestones and up to \$730.0 million upon achievement of commercialization milestones.

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

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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. 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 up to \$100,000,000 of common stock and warrants to purchase common stock in one or more offerings and in any combination. In addition, the selling stockholders may offer up to 8,600,000 shares of common stock in one or more offerings and in any combination. In this prospectus, we refer to the common stock and warrants collectively as securities. This prospectus provides you with a general description of the securities we and/or the selling stockholders may offer. A prospectus supplement, which we will provide in connection with each offering of the securities to the extent required by applicable law, will describe the specific amounts, prices and terms of the securities that we and/or the selling stockholders offer. We will also include in any prospectus supplement information, when applicable, about material U.S. federal income tax considerations relating to the securities, and the securities exchange, if any, on which the securities will be listed. This prospectus may not be used to consummate a sale of securities unless, to the extent required by applicable law, it is accompanied by a prospectus supplement.

Throughout this prospectus, when we refer to the shares of our common stock being registered on behalf of the selling stockholders, 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 stockholders in this prospectus, we are referring to the investors in the private placements who are named in this prospectus as the selling stockholders and, as applicable, any donees, pledgees, transferees or other successors-in-interest selling shares received after the date of this prospectus from the selling stockholders as a gift, pledge, or other non-sale related transfer.

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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 14,900,000 shares of series A convertible preferred stock to Isis and Alnylam in exchange for the membership interests such investors held 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 10,000,000 shares of series A convertible preferred stock to Isis and Alnylam at a purchase price of \$2.00 per share, for aggregate gross proceeds of \$20.0 million. In connection with the foregoing transactions, we entered into a Founding Investor Rights Agreement with Isis and Alnylam pursuant to which we granted certain registration rights to Isis and Alnylam. Upon completion of our initial public offering, the foregoing shares were converted into an aggregate of 12,450,000 shares of our common stock.

On October 10, 2012, pursuant to the terms of a Common Stock Purchase Agreement, we sold and issued 6,250,000 shares of our common stock to AstraZeneca at a price of \$4.00 per share. On October 10, 2012, we also entered into an Investor Rights Agreement with AstraZeneca pursuant to which we granted certain registration rights to AstraZeneca.

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(2) of, and Regulation D promulgated under, the Securities Act.

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RISK FACTORS

Investing in our securities 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 securities.

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 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, 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 our research and development activities, preclinical studies and future clinical trials;

our ability to obtain and maintain regulatory approval of our future 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 future product candidates;

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

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

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

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

our ability to successfully commercialize our future product candidates;

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

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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 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;

our use of the proceeds from our initial public offering and concurrent private placement or our subsequent public offering in July 2013; 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.

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USE OF PROCEEDS

Unless otherwise provided in any applicable prospectus supplement, we currently intend to use the net proceeds from the sale of the securities offered by us under this prospectus for general corporate purposes, including preclinical and clinical development of our clinical candidates, RG-101 and RG-012, and our other initial *microRNA* development candidates, 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 may set forth additional information on the use of proceeds from the sale of securities 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 any selling stockholder.

DILUTION

We will set forth in a prospectus supplement, when applicable, the following information regarding any material dilution of the equity interests of investors purchasing securities in an offering under this prospectus:

the net tangible book value per share of our equity securities before and after the offering;

the amount of the increase in such net tangible book value per share attributable to the cash payments made by purchasers in the offering; and

the amount of the immediate dilution from the public offering price which will be absorbed by such purchasers.

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DESCRIPTION OF SECURITIES

The descriptions of the securities contained in this prospectus, together with any applicable prospectus supplements, summarize the material terms and provisions of the various types of securities that we and/or the selling stockholders may offer. We will describe in any applicable prospectus supplement relating to any securities the particular terms of the securities offered by that prospectus supplement. If we so indicate in any applicable prospectus supplement, the terms of the securities may differ from the terms we have summarized below. We will also include in any prospectus supplement information, where applicable, about material U.S. federal income tax considerations relating to the securities, and the securities exchange, if any, on which the securities will be listed.

DESCRIPTION OF COMMON 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 stockholders 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.

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 February 28, 2014, we had 43,220,599 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 stockholders may offer in more detail in a prospectus supplement relating to the offering of shares of common stock to the extent required by applicable law. If we so indicate in a prospectus supplement, the terms of any common stock offered under that prospectus supplement may differ from the terms described below.

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

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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 February 28, 2014, there are no shares of preferred stock outstanding and we have no current plans to issue any shares of preferred stock.

Registration Rights

Under our investor rights agreements and registration rights agreement entered into in connection with private placements of our common stock and our preferred stock that converted to common stock in connection with our initial public offering, the holders of 20,003,780 shares of common stock, or their transferees, have the right to require us to register their shares with the SEC so that those shares may be publicly resold, or to include their shares in any registration statement we file.

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 obtained waivers of any and all rights to have shares registered under this registration statement from all holders of such registration rights.

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.

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Expiration of Registration Rights. With respect to 18,700,000 shares, the piggyback and Form S-3 registration rights discussed above will terminate in October 2015, three years following the closing of our initial public offering or, as to a given holder of registrable securities, when such holder is able to sell all of their registrable securities in a single 90-day period under Rule 144 of the Securities Act. With respect to 1,303,780 shares, the piggyback and Form S-3 registration rights discussed above will terminate in February 2018.

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

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

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

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

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

Section 203 defines a business combination to include:

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

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

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

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

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

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

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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.

DESCRIPTION OF WARRANTS

The following description, together with the additional information we may include in any applicable prospectus supplements, summarizes the material terms and provisions of the warrants that we may offer under this prospectus and the related warrant agreements and warrant certificates. While the terms summarized below will apply generally to any warrants that we may offer, we will describe the particular terms of any series of warrants in more detail in the applicable prospectus supplement. If we so indicate in the prospectus supplement, the terms of any warrants offered under that prospectus supplement may differ from the terms described below. Specific warrant agreements will contain additional important terms and provisions and will be incorporated by reference as an exhibit to the registration statement that includes this prospectus.

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General

We may issue warrants to purchase common stock in one or more series. We may issue warrants independently or together with common stock, and the warrants may be attached to or separate from these securities.

We will evidence each series of warrants by warrant certificates that we will issue under a separate agreement. We may enter into the warrant agreement with a warrant agent. We will indicate the name and address and other information regarding the warrant agent in the applicable prospectus supplement relating to a particular series of warrants.

If we decide to issue warrants pursuant to this prospectus, we will specify in a prospectus supplement the terms of the series of warrants, including, if applicable, the following:

the offering price and aggregate number of warrants offered;

the currency for which the warrants may be purchased;

the designation and terms of the securities with which the warrants are issued and the number of warrants issued with each such security or each principal amount of such security;

the date on and after which the warrants and the related securities will be separately transferable;

the number of shares of common stock purchasable upon the exercise of the warrants and the price at which these shares may be purchased upon such exercise;

the effect of any merger, consolidation, sale or other disposition of our business on the warrant agreement and the warrants;

the terms of any rights to redeem or call the warrants;

any provisions for changes to or adjustments in the exercise price or number of shares issuable upon exercise of the warrants;

the dates on which the right to exercise the warrants will commence and expire;

the manner in which the warrant agreement and warrants may be modified;

a discussion of any material U.S. income tax consequences of holding or exercising the warrants;

the terms of the securities issuable upon exercise of the warrants; and

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any other specific terms, preferences, rights or limitations of or restrictions on the warrants.

Before exercising their warrants, holders of warrants will not have any of the rights of holders of the common stock purchasable upon such exercise, including the right to receive dividends, if any, or payments upon our liquidation, dissolution or winding up or to exercise voting rights, if any.

Exercise of Warrants

Each warrant will entitle the holder to purchase the number of shares of common stock that we specify in the applicable prospectus supplement at the exercise price that we describe in the applicable prospectus supplement. Unless we otherwise specify in the applicable prospectus supplement, holders of the warrants may exercise the warrants at any time up to the expiration date that we set forth in the applicable prospectus supplement. After the close of business on the expiration date, unexercised warrants will become void.

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Holders of the warrants may exercise the warrants by delivering the warrant certificate representing the warrants to be exercised together with specified information, and paying the required amount to the warrant agent in immediately available funds, as provided in the applicable prospectus supplement. We will set forth on the reverse side of the warrant certificate and in the applicable prospectus supplement the information that the holder of the warrant will be required to deliver to the warrant agent.

Upon receipt of the required payment and the warrant certificate properly completed and duly executed at the corporate trust office of the warrant agent or any other office indicated in the applicable prospectus supplement, we will issue and deliver the securities purchasable upon such exercise. If fewer than all of the warrants represented by the warrant certificate are exercised, then we will issue a new warrant certificate for the remaining amount of warrants. If we so indicate in the applicable prospectus supplement, holders of the warrants may surrender securities as all or part of the exercise price for warrants.

Enforceability of Rights by Holders of Warrants

Each warrant agent will act solely as our agent under the applicable warrant agreement and will not assume any obligation or relationship of agency or trust with any holder of any warrant. A single bank or trust company may act as warrant agent for more than one issue of warrants. A warrant agent will have no duty or responsibility in case of any default by us under the applicable warrant agreement or warrant, including any duty or responsibility to initiate any proceedings at law or otherwise, or to make any demand upon us. Any holder of a warrant may, without the consent of the related warrant agent or the holder of any other warrant, enforce by appropriate legal action its right to exercise, and receive the securities purchasable upon exercise of, its warrants.

LEGAL OWNERSHIP OF SECURITIES

We can issue securities in registered form or in the form of one or more global securities. We describe global securities in greater detail below. We refer to those persons who have securities registered in their own names on the books that we or any applicable trustee maintain for this purpose as the **holders** of those securities. These persons are the legal holders of the securities. We refer to those persons who, indirectly through others, own beneficial interests in securities that are not registered in their own names, as **indirect holders** of those securities. As we discuss below, indirect holders are not legal holders, and investors in securities issued in book-entry form or in street name will be indirect holders.

Book-Entry Holders

We may issue securities in book-entry form only, as we will specify in any applicable prospectus supplement. This means securities may be represented by one or more global securities registered in the name of a financial institution that holds them as depositary on behalf of other financial institutions that participate in the depositary's book-entry system. These participating institutions, which are referred to as participants, in turn, hold beneficial interests in the securities on behalf of themselves or their customers.

Only the person in whose name a security is registered is recognized as the holder of that security. Securities issued in global form will be registered in the name of the depositary or its nominee. Consequently, for securities issued in global form, we will recognize only the depositary as the holder of the securities, and we will make all payments on the securities to the

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depository. The depository passes along the payments it receives to its participants, which in turn pass the payments along to their customers who are the beneficial owners. The depository and its participants do so under agreements they have made with one another or with their customers; they are not obligated to do so under the terms of the securities.

As a result, investors in a book-entry security will not own securities directly. Instead, they will own beneficial interests in a global security, through a bank, broker or other financial institution that participates in the depository's book-entry system or holds an interest through a participant. As long as the securities are issued in global form, investors will be indirect holders, and not holders, of the securities.

Street Name Holders

We may terminate a global security or issue securities in non-global form. In these cases, investors may choose to hold their securities in their own names or in street name. Securities held by an investor in street name would be registered in the name of a bank, broker or other financial institution that the investor chooses, and the investor would hold only a beneficial interest in those securities through an account he or she maintains at that institution.

For securities held in street name, we will recognize only the intermediary banks, brokers and other financial institutions in whose names the securities are registered as the holders of those securities, and we will make all payments on those securities to them. These institutions pass along the payments they receive to their customers who are the beneficial owners, but only because they agree to do so in their customer agreements or because they are legally required to do so. Investors who hold securities in street name will be indirect holders, not holders, of those securities.

Legal Holders

Our obligations, as well as the obligations of any applicable trustee and of any third parties employed by us or a trustee, run only to the legal holders of the securities. We do not have obligations to investors who hold beneficial interests in global securities, in street name or by any other indirect means. This will be the case whether an investor chooses to be an indirect holder of a security or has no choice because we are issuing the securities only in global form. For example, once we make a payment or give a notice to the holder, we have no further responsibility for the payment or notice even if that holder is required, under agreements with depository participants or customers or by law, to pass it along to the indirect holders but does not do so.

Special Considerations For Indirect Holders

If you hold securities through a bank, broker or other financial institution, either in book-entry form or in street name, you should check with your own institution to find out:

how it handles securities payments and notices;

whether it imposes fees or charges;

how it would handle a request for the holders' consent, if ever required;

whether and how you can instruct it to send you securities registered in your own name so you can be a holder, if that is permitted in the future;

how it would exercise rights under the securities if there were a default or other event triggering the need for holders to act to protect their interests; and

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if the securities are in book-entry form, how the depositary's rules and procedures will affect these matters.

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Global Securities

A global security is a security held by a depository that represents one or any other number of individual securities. Generally, all securities represented by the same global securities will have the same terms.

Each security issued in book-entry form will be represented by a global security that we deposit with and register in the name of a financial institution or its nominee that we select. The financial institution that we select for this purpose is called the depository. Unless we specify otherwise in any applicable prospectus supplement, The Depository Trust Company, or DTC, will be the depository for all securities issued in book-entry form.

A global security may not be transferred to or registered in the name of anyone other than the depository, its nominee or a successor depository, unless special termination situations arise. We describe those situations below under **Special Situations When a Global Security Will Be Terminated**. As a result of these arrangements, the depository, or its nominee, will be the sole registered owner and holder of all securities represented by a global security, and investors will be permitted to own only beneficial interests in a global security. Beneficial interests must be held by means of an account with a broker, bank or other financial institution that in turn has an account with the depository or with another institution that does. Thus, an investor whose security is represented by a global security will not be a holder of the security, but only an indirect holder of a beneficial interest in the global security.

If a prospectus supplement for a particular security indicates that the security will be issued in global form only, then the security will be represented by a global security at all times unless and until the global security is terminated. If termination occurs, we may issue the securities through another book-entry clearing system or decide that the securities may no longer be held through any book-entry clearing system.

Special Considerations For Global Securities

As an indirect holder, an investor's rights relating to a global security will be governed by the account rules of the investor's financial institution and of the depository, as well as general laws relating to securities transfers. We do not recognize an indirect holder as a holder of securities and instead deal only with the depository that holds the global security.

If securities are issued only in the form of a global security, an investor should be aware of the following:

an investor cannot cause the securities to be registered in his or her name, and cannot obtain non-global certificates for his or her interest in the securities, except in the special situations we describe below;

an investor will be an indirect holder and must look to his or her own bank or broker for payments on the securities and protection of his or her legal rights relating to the securities, as we describe under **Legal Holders** above;

an investor may not be able to sell interests in the securities to some insurance companies and to other institutions that are required by law to own their securities in non-book-entry form;

an investor may not be able to pledge his or her interest in a global security in circumstances where certificates representing the securities must be delivered to the lender or other beneficiary of the pledge in order for the pledge to be effective;

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the depositary's policies, which may change from time to time, will govern payments, transfers, exchanges and other matters relating to an investor's interest in a global security. We and any applicable trustee have no responsibility for any aspect of the depositary's actions or for its records of ownership interests in a global security. We and the trustee also do not supervise the depositary in any way;

the depositary may, and we understand that DTC will, require that those who purchase and sell interests in a global security within its book-entry system use immediately available funds, and your broker or bank may require you to do so as well; and

financial institutions that participate in the depositary's book-entry system, and through which an investor holds its interest in a global security, may also have their own policies affecting payments, notices and other matters relating to the securities.

There may be more than one financial intermediary in the chain of ownership for an investor. We do not monitor and are not responsible for the actions of any of those intermediaries.

Special Situations When A Global Security Will Be Terminated

In a few special situations described below, the global security will terminate and interests in it will be exchanged for physical certificates representing those interests. After that exchange, the choice of whether to hold securities directly or in street name will be up to the investor. Investors must consult their own banks or brokers to find out how to have their interests in securities transferred to their own name, so that they will be direct holders. We have described the rights of holders and street name investors above.

The global security will terminate when the following special situations occur:

if the depositary notifies us that it is unwilling, unable or no longer qualified to continue as depositary for that global security and we do not appoint another institution to act as depositary within 90 days;

if we notify any applicable trustee that we wish to terminate that global security; or

if an event of default has occurred with regard to securities represented by that global security and has not been cured or waived. A prospectus supplement may also list additional situations for terminating a global security that would apply only to the particular series of securities covered by such prospectus supplement. When a global security terminates, the depositary, and not we or any applicable trustee, is responsible for deciding the names of the institutions that will be the initial direct holders.

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This prospectus relates to the resale by the selling stockholders named herein of up to 8,600,000 shares of our common stock. For more information, see [Summary Private Placements](#) above.

As of February 28, 2014, the selling stockholders named below were our three largest stockholders. Isis and Alnylam each have one representative on our board of directors, and until November 5, 2012, each had two representatives on our board of directors. In addition, we have formed strategic alliances with each of the selling stockholders named in the table below. In September 2007, we entered into a license and collaboration agreement with Alnylam and Isis, which we subsequently amended, restated and superseded in January 2009, and further amended in June 2010, October 2011 and August 2013. In August 2012, we entered into a collaboration and license agreement with AstraZeneca. These agreements are described in our annual report for the year ended December 31, 2013, filed with the SEC on February 28, 2014 (File No. 001-35670), and are incorporated herein by reference.

This table below was prepared based on information supplied to us by the selling stockholders and reflects holdings as of February 28, 2014. As used in this prospectus, the term [selling stockholders](#) includes each of the selling stockholders listed below, and any donees, pledges, transferees or other successors in interest selling shares received after the date of this prospectus from a 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 all of the shares that a selling stockholder may offer under this prospectus. The selling stockholders may sell some, all or none of their shares. The selling stockholders 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 16. We do not know how long the selling stockholders will hold the shares before selling them, and we currently have no agreements, arrangements or understandings with the selling stockholders regarding the sale of any of the shares.

The percentage ownership information after the offering is based on 43,220,599 shares of our common stock outstanding as of February 28, 2014. 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(1)	Shares of Common Stock Beneficially Owned Before Offering	Number of Shares Being Offered	Shares of Common Stock Beneficially Owned Following the Offering	
			Number	% of Class
Isis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, CA 92010	7,074,500(1)	3,524,750	3,549,750	8.2%
AstraZeneca AB SE 431 83 Molndal Sweden	6,250,000	2,000,000	4,250,000	9.8%
Alnylam Pharmaceuticals, Inc. 300 Third Street, 3 rd Floor Cambridge, MA 02142	6,150,500	3,075,250	3,075,250	7.1%

(1) Includes 25,000 shares that Stanley T. Croke, M.D., Ph.D., one of our former directors, has the right to acquire from us within 60 days of February 28, 2014 pursuant to the exercise of stock options.

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PLAN OF DISTRIBUTION

We or the selling stockholders may sell the securities 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 stockholders may sell the securities to or through underwriters or dealers, through agents, or directly to one or more purchasers. We may distribute securities from time to time in one or more transactions:

at a fixed price or prices, which may be changed;

at market prices prevailing at the time of sale;

at prices related to such prevailing market prices; or

at negotiated prices.

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 securities, including, to the extent applicable:

the name or names of the underwriters, if any;

the purchase price of the securities 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 securities 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 securities may be listed.

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

If underwriters are used in the sale, they will acquire the securities for their own account and may resell the securities 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 securities will be subject to the conditions set forth in the applicable underwriting agreement. We or the selling stockholders may offer the securities 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 securities offered by an applicable prospectus supplement, other than securities covered by any over-allotment option. Any public offering price and any discounts or concessions allowed or reallocated or paid to dealers may change from time to time. We or the selling stockholders 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.

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

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We or the selling stockholders may authorize agents or underwriters to solicit offers by certain types of institutional investors to purchase securities from us or the selling stockholders 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 stockholders must pay for solicitation of these contracts in an applicable prospectus supplement.

We or the selling stockholders 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 stockholders in the ordinary course of business.

All securities we may offer, other than common stock, will be new issues of securities with no established trading market. Any underwriters may make a market in these securities, but will not be obligated to do so and may discontinue any market making at any time without notice. We cannot guarantee the liquidity of the trading markets for any securities.

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 security so long as the stabilizing bids do not exceed a specified maximum price. Syndicate-covering or other short-covering transactions involve purchases of the securities, 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 securities 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 securities 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 that are qualified market makers on the Nasdaq Global Select Market engage in passive market making transactions in the common stock on the Nasdaq Global Select Market accordance with Regulation M under the Exchange Act, 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 security; 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 securities 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 securities offered pursuant to this prospectus and any applicable prospectus supplement.

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LEGAL MATTERS

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

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2013, as set forth in their report, which is incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

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

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

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

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

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

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

- (1) our Annual Report on Form 10-K for the year ended December 31, 2013, as filed with the SEC on February 28, 2014;

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- (2) the information specifically incorporated by reference into our Annual Report on Form 10-K for the year ended December 31, 2013 from our definitive proxy statement on Schedule 14A filed with the SEC on April 11, 2014;

- (3) our Current Reports on Form 8-K filed with the SEC on February 5, 2014 and March 11, 2014; and

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

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

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\$80,000,000

Common Stock

PROSPECTUS SUPPLEMENT

Joint Book-Running Managers

Deutsche Bank Securities

BMO Capital Markets

Co-Managers

Needham & Company

WedBush PacGrow Life Sciences

FBR

October , 2014