Regulus Therapeutics Inc.
Form S-1/A
July 09, 2013
Table of Contents

**As filed with the Securities and Exchange Commission on July 9, 2013**

**Registration No. 333-189607**

# UNITED STATES

# SECURITIES AND EXCHANGE COMMISSION

**Washington, D.C. 20549**

# AMENDMENT NO. 1

# TO

# FORM S-1

# REGISTRATION STATEMENT

***UNDER***

***THE SECURITIES ACT OF 1933***

# Regulus Therapeutics Inc.

**(Exact Name of Registrant as Specified in Its Charter)**

| Delaware<br>(State or Other Jurisdiction of<br><br>Incorporation or Organization) | 2834<br>(Primary Standard Industrial<br><br>Classification Code Number) | 26-4738379<br>(I.R.S. Employer<br><br>Identification Number) |
|---|---|---|

**3545 John Hopkins Ct.**

**Suite 210**

**San Diego, CA 92121**

**(858) 202-6300**

**(Address, Including Zip Code, and Telephone Number, Including Area Code, of Registrant s Principal Executive Offices)**

**Kleanthis G. Xanthopoulos, Ph.D.**

**President and Chief Executive Officer**

**Regulus Therapeutics Inc.**

**3545 John Hopkins Court**

**Suite 210**

**San Diego, CA 92121**

**(858) 202-6300**

**(Name, Address, Including Zip Code, and Telephone Number, Including Area Code, of Agent for Service)**

***Copies to:***

| **Thomas A. Coll, Esq.**<br><br>**Kenneth J. Rollins, Esq.**<br><br>**Cooley LLP** | **Mitchell S. Bloom, Esq.**<br><br>**Maggie L. Wong, Esq.**<br><br>**Goodwin Procter LLP** |
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| | |
|---|---|
| **4401 Eastgate Mall** | **53 State Street** |
| **San Diego, CA 92121** | **Boston, MA 02109** |
| **(858) 550-6000** | **(617) 570-1000** |

**Approximate date of commencement of proposed sale to the public:**

As soon as practicable after the effective date of this registration statement.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, as amended (the Securities Act ), check the following box. ¨

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

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

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

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

| | | | |
|---|---|---|---|
| Large accelerated filer | ¨ | Accelerated filer | ¨ |
| Non-accelerated filer | ¨ (Do not check if a smaller reporting company) | Smaller reporting company | x |

**CALCULATION OF REGISTRATION FEE**

| **Title of each class of securities to be registered** | **Proposed maximum aggregate offering price (1)** | **Amount of registration fee** |
|---|---|---|
| Common Stock, $0.001 par value per share | $57,960,000 | $7,905.75 (2) |

(1) Estimated solely for the purpose of calculating the amount of the registration fee in accordance with Rule 457(o) under the Securities Act. Includes the offering price of shares that the underwriters have the option to purchase to cover over-allotments, if any.

(2) Of which $7,843.00 was previously paid.

**The Registrant hereby amends this registration statement on such date or dates as may be necessary to delay its effective date until the Registrant shall file a further amendment that specifically states that this registration statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933, as amended, or until the registration statement shall become effective on such date as the Securities and Exchange Commission, acting pursuant to said Section 8(a), may determine.**

Table of Contents

**The information in this prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell these securities and we are not soliciting offers to buy these securities in any jurisdiction where the offer or sale is not permitted.**

**PRELIMINARY PROSPECTUS SUBJECT TO COMPLETION, DATED JULY 9, 2013**

# 4,500,000 Shares

# Common Stock

Regulus Therapeutics Inc. is offering 4,500,000 shares of its common stock. Our common stock is listed on The NASDAQ Global Market under the symbol RGLS. On July 8, 2013, the last reported sale price of our common stock on The NASDAQ Global Market was $11.20 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 and future filings.

**Investing in our common stock involves substantial risks. See Risk factors beginning on page 12.**

# PRICE $ A SHARE

| | Per Share | Total |
|---|---|---|
| Public offering price | $ | $ |
| Underwriting discounts and commissions | $ | $ |
| Proceeds, before expenses, to us | $ | $ |

We have granted the underwriters an option for 30 days from the date of this prospectus to purchase up to 675,000 of additional shares of our common stock to cover over-allotments. If the underwriters exercise the option in full, the total underwriting discounts and commissions payable by us will be $ , and the total proceeds to us, before expenses, will be $ .

The Securities and Exchange Commission and state securities regulators have not approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The underwriters expect to deliver the shares of common stock to purchasers on , 2013.

**Lazard Capital Markets** **Cowen and Company** **BMO Capital Markets**

**Needham & Company** **Wedbush PacGrow Life Sciences**

**The date of this prospectus is , 2013**

Table of Contents

**TABLE OF CONTENTS**



**You should rely only on the information contained in this prospectus and in any free writing prospectus that we may have provided to you in connection with this offering. Neither we nor any of the underwriters has authorized anyone to provide you with information different from, or in addition to, that contained in this prospectus or any such free writing prospectus. If anyone provides you with different or inconsistent information, you should not rely on it. Neither we nor any of the underwriters is making an offer to sell or seeking offers to buy shares of our common stock in any jurisdiction where or to any person to whom the offer or sale is not permitted. The information in this prospectus is accurate only as of the date on the front cover of this prospectus and the information in any free writing prospectus that we may have provided to you in connection with this offering is accurate only as of the date of that free writing prospectus. Our business, financial condition, results of operations and future growth prospects may have changed since those dates.**

For investors outside the United States: neither we nor any of the underwriters has done anything that would permit this offering or possession or distribution of this prospectus or any free writing prospectus we may provide to you in connection with this offering in any jurisdiction where action for that purpose is required, other than in the United States. You are required to inform yourselves about and to observe any restrictions relating to this offering and the distribution of this prospectus and any such free writing prospectus outside of the United States.

Table of Contents

# Prospectus summary

*This summary provides an overview of selected information contained elsewhere in this prospectus or incorporated by reference into this prospectus from our Annual Report on Form 10-K for the year ended December 31, 2012 and our other filings with the Securities and Exchange Commission listed in the section of this prospectus entitled Incorporation of certain information by reference and does not contain all of the information you should consider before investing in our common stock. You should carefully read this prospectus, the registration statement of which this prospectus is a part and the information incorporated by reference herein in their entirety before investing in our common stock, including the information discussed under Risk factors in this prospectus and in our Annual Report on Form 10-K for the year ended December 31, 2012 and our Quarterly Report on Form 10-Q for the quarter ended March 31, 2013 incorporated by reference herein, along with our financial statements and notes thereto that are incorporated by reference herein. Unless otherwise indicated herein, the terms Regulus, we, our, us, or the Company refer to Regulus Therapeutics Inc.*

**OVERVIEW**

We are a biopharmaceutical company focused on discovering and developing first-in-class drugs that target *micro*RNAs 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 *micro*RNAs pursuant to a license and collaboration agreement. *micro*RNAs 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 *micro*RNAs is directly linked to many diseases. We believe we have assembled the leading position in the *micro*RNA field, including expertise in *micro*RNA 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 *micro*RNA product platform. We are using our *micro*RNA product platform to develop chemically modified, single-stranded oligonucleotides that we call anti-miRs. We use these anti-miRs to modulate *micro*RNAs and by doing so return diseased cells to their healthy state. We believe *micro*RNAs 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.

We are currently optimizing anti-miRs in several distinct programs, both independently and with our strategic alliance partners, AstraZeneca AB, or AstraZeneca, GlaxoSmithKline plc, or GSK, and Sanofi. We also have a collaboration agreement with Biogen Idec MA Inc., or Biogen Idec, to evaluate the potential use of *micro*RNA signatures as a biomarker for human patients with multiple sclerosis. Under these strategic alliances, we are eligible to receive up to approximately $1.3 billion in milestone payments upon successful commercialization of *micro*RNA therapeutics for the programs contemplated by our agreements. These payments include up to $42.0 million upon achievement of preclinical and IND milestones, up to $272.0 million upon achievement of clinical development milestones, up to $305.0 million upon achievement of regulatory milestones and up to $670.0 million upon achievement of commercialization milestones.

We are currently executing on our Road to the Clinic strategy which sets forth certain corporate goals that seek to advance our *micro*RNA therapeutic pipeline towards the clinic. Specifically, we set the goal of nominating two *micro*RNA candidates for clinical development in 2013. In May 2013, we announced our first clinical candidate, RG-101, for which we have full ownership and commercial rights. RG-101 is a GalNAc-conjugated *micro*RNA anti-miR, which targets *micro*RNA-122, for the treatment of patients with chronic hepatitis C virus infection, or HCV. We expect to submit our first investigational new drug

Table of Contents

application, or IND, to the U.S. Food and Drug Administration, or FDA, or equivalent foreign regulatory filing with foreign regulatory authorities, as applicable, for RG-101 in the first half of 2014. We anticipate that we will nominate a second clinical development candidate by the end of 2013.

**POTENTIAL OF *micro*RNA BIOLOGY**

RNA plays an essential role in the process used by cells to encode and translate genetic information from DNA to proteins. RNA is comprised of subunits called nucleotides and is synthesized from a DNA template by a process known as transcription. Transcription generates different types of RNA, including messenger RNAs that carry the information for proteins in the sequence of their nucleotides. In contrast, *micro*RNAs are small RNAs that do not code for proteins but rather are responsible for regulating gene expression by affecting the translation of target messenger RNAs. By interacting with many messenger RNAs, a single *micro*RNA can regulate several genes that are instrumental for the normal function of a biological pathway. More than 500 *micro*RNAs have been identified to date in humans, each of which is believed to interact with a specific set of genes that control key aspects of cell biology. Since most diseases are multi-factorial and involve multiple targets in a pathway, the ability to modulate gene networks by targeting a single *micro*RNA provides a new therapeutic approach for treating complex diseases.

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

- *micro*RNAs are a recent discovery in biology and, up until now, have not been a focus of pharmaceutical research;
- *micro*RNAs play a critical role in regulating biological pathways by controlling the translation of many target genes;
- *micro*RNA therapeutics target entire disease pathways which may result in more effective treatment of complex multi-factorial diseases;
- *micro*RNA therapeutics can be produced with a more efficient rational drug design process; and
- *micro*RNA therapeutics may be synergistic with other therapies because of their different mechanism of action.

**OUR *micro*RNA PRODUCT PLATFORM**

We are the leading company in the field of *micro*RNA therapeutics. Backed by our founding companies, Alnylam and Isis, we are uniquely positioned to leverage oligonucleotide technologies that have been proven in clinical trials. Central to achieving our goals is the know-how that we have accumulated in oligonucleotide design and how the specific chemistries behave in the clinical setting. We refer to this collective know-how, proprietary technology base, and its systematic application as our *micro*RNA product platform.

We view the following as providing a competitive advantage for our *micro*RNA product platform:

- a mature platform selectively producing multiple development candidates advancing to the clinic;
- scientific advisors who are pioneers in the *micro*RNA field;
- access to proven RNA therapeutic technologies through our founding companies, as well as approximately 900 patents and patent applications relating to oligonucleotide technologies;

- a leading *micro*RNA intellectual property estate with access to over 170 patents and patent applications covering compositions and therapeutic uses;

Table of Contents

- development expertise and financial resources provided by our three major strategic alliances with AstraZeneca, GSK and Sanofi; and

- over 30 academic collaborations that help us identify new *micro*RNA targets and support our early stage discovery efforts.

The disciplined approach we take for the discovery and development of *micro*RNA therapeutics is as important as the assets assembled to execute our plans and is based on the following four steps:

*Step 1 - Evaluation of microRNA therapeutic opportunities*

The initiation of our *micro*RNA discovery and development efforts is based on rigorous scientific and business criteria, including:

- existence of significant scientific evidence to support the role of a specific *micro*RNA in a disease;

- availability of predictive preclinical disease models to test our *micro*RNA development candidates;

- ability to effectively deliver anti-miRs to the diseased cells or tissues; and

- existence of a reasonable unmet medical need and commercial opportunity.

*Step 2 - Identification of microRNA targets*

We identify *micro*RNA targets through bioinformatic analysis of public and proprietary *micro*RNA expression profiling data sets from samples of diseased human tissues. The analysis of such data sets can immediately highlight a potential role for specific *micro*RNAs in the disease being studied. Further investigation of animal models that are predictive of human diseases in which those same *micro*RNAs are also dysregulated provides additional data to support a new program. We have applied this strategy successfully in our existing programs and we believe that this approach will continue to help us identify clinically relevant *micro*RNA targets.

*Step 3 - Validation of microRNA targets*

Our validation strategy is based on two distinct steps. First, using genetic tools, we determine whether up-regulation, or overproduction, of the *micro*RNA in healthy animals can create the specific disease state and inhibition of the *micro*RNA can lead to a therapeutic benefit. Second, using animal models predictive of human diseases, we determine whether pharmacological modulation of the up-regulated *micro*RNA target with our anti-miRs can also lead to a therapeutic benefit. This validation process enables us to prioritize the best *micro*RNA targets that appear to be key drivers of disease and not simply correlating markers.

*Step 4 - Optimization of microRNA development candidates*

We have developed a proprietary process that allows us to rapidly generate an optimized development candidate. Unlike traditional drug classes, such as small molecules, in which thousands of compounds must be screened to identify prospective leads, the fact that anti-miRs are mirror images of their target *micro*RNAs allows for a more efficient rational design process. The optimization process incorporates our extensive knowledge base around oligonucleotide chemistry and anti-miR design to efficiently synthesize a starting pool of rationally designed anti-miRs to be evaluated in a series of proven assays and models. We also enhance our anti-miRs for distribution to the tissues where the specific *micro*RNA target is causing disease.

**OUR INITIAL DEVELOPMENT CANDIDATES**

We are developing single-stranded oligonucleotides, which are chemically synthesized chains of nucleotides that are mirror images of specific target *micro*RNAs. We incorporate proprietary chemical modifications to enhance drug properties such as potency, stability and tissue distribution. We refer to

Table of Contents

these chemically modified oligonucleotides as anti-miRs. Each anti-miR is designed to bind with and inhibit a specific *micro*RNA target that is up-regulated in a cell and that is involved in the disease state. In binding to the *micro*RNA, anti-miRs correct the dysregulation and return diseased cells to their healthy state. We have demonstrated therapeutic benefits of our anti-miRs in at least 20 different preclinical models of human diseases.

We have identified and validated several *micro*RNA targets across a number of disease categories and are working independently and with our strategic alliance partners to optimize anti-miR development candidates. We expect that anti-miR development candidates will be easily formulated in saline solution and administered systemically or locally depending on the therapeutic indication. Our distinct therapeutic development programs are shown in the table below:

| ***micro*RNA *target*** | **anti-miR program** | **Commercial rights** |
|---|---|---|
| miR-122 | RG-101 for HCV | Regulus* |
| miR-221 | Hepatocellular carcinoma | Regulus |
| miR-10b | Glioblastoma | Regulus |
| miR-21 | Hepatocellular carcinoma | Sanofi |
| miR-21 | Kidney fibrosis | Sanofi |
| miR-33 | Atherosclerosis | AstraZeneca |

* With the exception of RG-101, commercial rights for miR-122 target licensed to GSK.

One aspect of our strategy is to pursue a balanced approach between product candidates that we develop ourselves and those that we develop with partners. We intend to focus our own resources on proprietary product opportunities in therapeutic areas where development and commercialization activities are appropriate for our size and financial resources, which we anticipate will include niche indications and orphan diseases. In therapeutic areas where costs are more significant, development timelines are longer or markets are too large for our capabilities, we will seek to secure partners with requisite expertise and resources.

Our approach has been validated to date by the following strategic alliances and collaborations with large pharmaceutical companies:

- In April 2008, we formed a strategic alliance with GSK to discover and develop *micro*RNA therapeutics for immuno-inflammatory diseases. In February 2010, we and GSK expanded the alliance to include potential *micro*RNA therapeutics for the treatment of HCV. In June 2013, we amended our agreement with GSK and agreed that RG-101 is fully-owned by us and that miR-122 remains a collaboration target under the agreement.

- In June 2010, we formed a strategic alliance with Sanofi to discover and develop *micro*RNA therapeutics for fibrotic diseases. In July 2012, we expanded the alliance to include potential *micro*RNA therapeutics in oncology. The original research term for this strategic alliance expired in June 2013, upon which we and Sanofi entered into an option agreement pursuant to which we granted Sanofi an exclusive right to negotiate the co-development and commercialization of certain of our unencumbered *micro*RNA programs through December 2013, for which Sanofi has agreed to pay us an upfront option fee of $2.5 million, $1.25 million of which is creditable against future amounts payable by Sanofi to us. In addition, Sanofi granted us an exclusive option, which also expires in December 2013 to negotiate the co-development and commercialization of miR-21.

- In August 2012, we formed a strategic alliance with AstraZeneca to discover and develop *micro*RNA therapeutics for cardiovascular diseases, metabolic diseases and oncology.

- In August 2012, we entered into a collaboration agreement with Biogen Idec to evaluate the potential use of *micro*RNA signatures as a biomarker for human patients with multiple sclerosis. In June 2013, we and Biogen Idec amended the collaboration agreement to update the research plan and criteria for success.

4

Table of Contents

**OUR STRATEGY**

We are building the leading biopharmaceutical company focused on the discovery and development of first-in-class, targeted drugs based on our proprietary *micro*RNA product platform. The key elements of our strategy are to:

- *Rapidly advance our initial programs into clinical development.* We are currently optimizing our proprietary and partnered anti-miRs for development candidate selection. Under our Road to the Clinic strategy, we have nominated our fully-owned compound, RG-101, for the treatment of HCV as our first clinical candidate and expect to submit our first IND, or equivalent foreign regulatory filing, for RG-101 in the first half of 2014. We anticipate that we will nominate a second clinical candidate by the end of 2013.

- *Focus our resources on developing drugs for niche indications or orphan diseases*. We believe that *micro*RNA therapeutics have utility in almost every disease state as they regulate pathways, not single targets. We intend to focus on proprietary product opportunities in niche therapeutic areas where the development and commercialization activities are appropriate for our size and financial resources.

- *Selectively form strategic alliances to augment our expertise and accelerate development and commercialization*. We have established strategic alliances with AstraZeneca, GSK and Sanofi and we will continue to seek partners who can bring therapeutic expertise, development and commercialization capabilities and funding to allow us to maximize the potential of our *micro*RNA product platform.

- *Selectively use our micro*RNA *product platform to develop additional targets.* We have identified several other *micro*RNA targets with potential for therapeutic modulation and will apply our rigorous scientific and business criteria to develop them.

- *Develop micro*RNA *biomarkers to support therapeutic product candidates*. We believe that *micro*RNA biomarkers may be used to select optimal patient segments in clinical trials, to develop companion diagnostics, and to monitor disease progression or relapse. We believe these *micro*RNA biomarkers can be applied toward drugs that we develop and drugs developed by other companies, including small molecules and monoclonal antibodies.

- *Maintain scientific and intellectual leadership in the microRNA field*. We will continue to conduct research in the *micro*RNA field to better understand this new biology and characterize the specific mechanism of action for our future drugs. This includes building on our strong network of key opinion leaders and securing additional intellectual property rights to broaden our existing proprietary asset estate.

**OUR LEADERSHIP**

Our management has more than 50 years of collective experience leading the discovery and development of innovative therapeutics, including significant operational and financial experience with emerging biotechnology companies, which we believe is the ideal combination of talent to execute our strategy. In addition, our experienced board of directors, which includes representatives of our founding companies, Alnylam and Isis, provides significant support and guidance in all aspects of our business.

Our executive officers are:

- Kleanthis G. Xanthopoulos, Ph.D., our President and Chief Executive Officer, is an entrepreneur who has been involved in founding several companies, including Anadys Pharmaceuticals, Inc. (acquired by F. Hoffmann-La Roche Inc. in 2011), which he started as President and Chief Executive Officer.

5

- Neil W. Gibson, Ph.D., our Chief Scientific Officer, is a leading scientist focused on cancer research and drug development who previously served as Chief Scientific Officer of the Oncology Research Unit at Pfizer Inc. and as Chief Scientific Officer of OSI Pharmaceuticals, Inc. He was involved in the development of several commercial cancer drugs including Xalkori® (crizotinib), Nexavar® (sorafenib) and Tarceva® (erlotinib).

Our executive team is supported by the following key personnel:

- Mary Glanville, our Senior Vice President of Human Capital, is an accomplished human resources executive in the life sciences industry who previously served in management roles at Anadys Pharmaceuticals, Inc. (acquired by F. Hoffman-La Roche Inc. in 2011), Inflazyme Inc. and Inex Pharmaceuticals Corp.

- Victor Knopov, Ph.D., our Vice President, Pharmaceutical Development, is a leader in oligonucleotide drug delivery and pharmaceutical development who has held positions at Nitto Denko Technical Corporation, Bio-Medics, Inc., EnGene, Inc., Marina Biotech, Inc. and Inex Pharmaceuticals Corporation. Dr. Knopov has extensive knowledge of Chemistry, Manufacturing and Control, or CMC, development for various technology platforms including commercial production of enzymes, anticancer liposomal products as well as advanced delivery systems for antisense, plasmids and siRNA based on lipids, polymer nanoparticles and conjugated systems.

- Daniel R. Chevallard, CPA, our Vice President, Finance and Accounting, is a corporate finance leader with public accounting expertise who previously held senior roles in corporate finance, accounting and financial reporting as a corporate controller and Senior Director, Finance at Prometheus Laboratories Inc. and who was a senior financial auditor at Ernst & Young LLP.

Our executive team, key personnel and board of directors are supported by our scientific advisory board members, who are renowned pioneers in the *micro*RNA field:

- David Baltimore, Ph.D., Chairman of our scientific advisory board and Professor of Biology at the California Institute of Technology, received the Nobel Prize in 1975 and is highly regarded as a pioneer in virology and immunology, with his current research investigating the role of *micro*RNAs in immunity. Dr. Baltimore is also a member of our board of directors.

- David Bartel, Ph.D., Professor of Biology at the Massachusetts Institute of Technology and the Whitehead Institute for Biomedical Research and an investigator at the Howard Hughes Medical Institute, studies *micro*RNA genomics, target recognition and regulatory functions.

- Gregory Hannon, Ph.D., Professor at the Cold Spring Harbor Laboratory and an investigator at the Howard Hughes Medical Institute, has identified and characterized many of the major biogenesis and effector complexes for *micro*RNA biology.

- Markus Stoffel, M.D., Ph.D., Professor of Metabolic Diseases at the Swiss Federal Institute of Technology, is focused on *micro*RNA research and the regulation of glucose and lipid metabolism.

- Thomas Tuschl, Ph.D., Professor and Head of the Laboratory for RNA Molecular Biology at the Rockefeller University and an investigator at the Howard Hughes Medical Institute, discovered many of the mammalian *micro*RNA genes and has developed methods for characterization of small RNAs.

Table of Contents

**RISKS ASSOCIATED WITH OUR BUSINESS**

Our business and ability to execute our business strategy are subject to a number of risks of which you should be aware before you decide to buy our common stock. In particular, you should consider the following risks, which are discussed more fully in the section entitled Risk factors in this prospectus and in our Annual Report on Form 10-K for the year ended December 31, 2012 and our Quarterly Report on Form 10-Q for the quarter ended March 31, 2013, incorporated by reference herein.

- We have never generated any revenue from product sales and may never become profitable. Even if this offering is successful, we may need to raise additional funds to support our operations and such funding may not be available to us on acceptable terms, or at all.

- The approach we are taking to discover and develop drugs is novel and may never lead to marketable products.

- All of our programs are still in preclinical development. Preclinical testing and clinical trials of our future product candidates may not be successful. If we are unable to successfully complete preclinical testing and clinical trials of our product candidates or experience significant delays in doing so, our business will be materially harmed.

- We will depend on our strategic alliances for the development and eventual commercialization of certain future *micro*RNA product candidates. If these strategic alliances are unsuccessful or are terminated, we may be unable to commercialize certain product candidates or generate future revenue from our development programs.

- If we are unable to obtain or protect intellectual property rights related to our future products and product candidates, we may not be able to effectively develop or commercialize any of our product candidates or otherwise compete effectively in our markets.

- We will need to expand our organization and we may experience difficulties in managing this growth, which could disrupt our operations.

- Our future success depends on our ability to retain key executives and to attract, retain and motivate qualified personnel and our failure to do so might impede the progress of our research, development and commercialization objectives.

**CORPORATE INFORMATION**

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

We use Regulus Therapeutics as a trademark in the United States and other countries. We have filed for registration of this trademark in the United States and have registered it in the 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.

7

Table of Contents

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.

Table of Contents

# The offering

| | |
|---|---|
| Common stock offered by us | 4,500,000 shares |
| Common stock to be outstanding after this offering | 40,465,371 shares |
| Over-allotment option | The underwriters have an option for a period of 30 days to purchase up to 675,000 additional shares of our common stock to cover over-allotments. |
| Use of proceeds | We intend to use the net proceeds of this offering for preclinical and clinical development of our proprietary compound, RG-101, and our other initial *micro*RNA development candidates, for the identification and validation of additional *micro*RNA targets and for other general corporate purposes. See Use of proceeds. |
| Risk factors | You should read the Risk factors section of this prospectus for a discussion of certain factors to consider carefully before deciding to purchase any shares of our common stock. |
| NASDAQ Global Market symbol | RGLS |

The number of shares of our common stock to be outstanding after this offering is based on 35,965,371 shares of common stock outstanding as of March 31, 2013, and excludes:

- 4,742,780 shares of common stock issuable upon the exercise of outstanding stock options as of March 31, 2013, at a weighted average exercise price of $2.24 per share;
- 2,191,925 shares of common stock reserved for future issuance under our 2012 equity incentive plan, or the 2012 Plan, plus any future increases in the number of shares of common stock reserved for issuance under the 2012 Plan pursuant to the evergreen provision; and
- 481,274 shares of common stock reserved for future issuance under our 2012 employee stock purchase plan, or the ESPP, plus any future increases in the number of shares of common stock reserved for issuance under the ESPP pursuant to the evergreen provision.

Unless otherwise indicated, all information contained in this prospectus, and the number of shares of common stock outstanding as of March 31, 2013 assumes no exercise by the underwriters of their over-allotment option to purchase up to an additional 675,000 shares of our common stock.

Table of Contents

# Summary financial data

The following table summarizes our financial data. We derived the summary statement of operations data for the years ended December 31, 2010, 2011 and 2012 from our audited financial statements and related notes incorporated by reference in this prospectus. We derived the summary statement of operations data for the three months ended March 31, 2012 and 2013 and balance sheet data as of March 31, 2013 from our unaudited financial statements and related notes incorporated by reference in this prospectus. Our historical results are not necessarily indicative of the results that may be expected in the future and results of interim periods are not necessarily indicative of the results for the entire year. The summary financial data should be read together with our financial statements and related notes incorporated by reference in this prospectus, Selected financial data and Management s discussion and analysis of financial condition and results of operations appearing elsewhere or incorporated by reference in this prospectus.

| | Year ended December 31, | | | Three months ended March 31, | |
|---|---|---|---|---|---|
| **Statement of operations data** | **2010** | **2011** | **2012** | **2012** | **2013** |
| | (in thousands, except share and per share data) | | | (unaudited) | |
| Revenues: | | | | | |
| Revenue under strategic alliances and collaborations | $ 8, | | | | |