Regulus Therapeutics Inc.
Form 424B4
July 17, 2013
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**Filed Pursuant to Rule 424(b)(4)**
**Registration No. 333-189607**

# 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 16, 2013, the last reported sale price of our common stock on The NASDAQ Global Market was $10.69 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 $9.50 A SHARE

| | Per Share | Total |
|---|---|---|
| Public offering price | $ 9.50 | $ 42,750,000 |
| Underwriting discounts and commissions (1) | $ 0.57 | $ 2,565,000 |
| Proceeds, before expenses, to us | $ 8.93 | $ 40,185,000 |

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

We have granted the underwriters an option for 30 days from the date of this prospectus to purchase up to 675,000 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 $2,949,750, and the total proceeds to us, before expenses, will be $46,212,750.

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 July 22, 2013.

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

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

**The date of this prospectus is July 16, 2013**

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**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.

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# 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

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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;

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- 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

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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 paid 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.

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**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.

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- 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.

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**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.

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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.

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# 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.

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# 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 | $ 8,112 | $ 13,767 | $ 12,700 | $ 3,344 | $ 3,238 |
| Grant revenue | 489 | 22 | | | |
| Total revenues | 8,601 | 13,789 | 12,700 | 3,344 | 3,238 |
| Operating expenses: | | | | | |
| Research and development | 20,178 | 17,289 | 20,342 | 4,603 | 6,883 |
| General and administrative | 3,921 | 3,637 | 4,932 | 921 | 1,905 |
| Total operating expenses | 24,099 | 20,926 | 25,274 | 5,524 | 8,788 |
| Loss from operations | (15,498) | (7,137) | (12,574) | (2,180) | (5,550) |
| Other expense, net | (91) | (259) | (4,844) | (66) | (1,689) |
| Loss before income taxes | (15,589) | (7,396) | (17,418) | (2,246) | (7,239) |
| Income tax (benefit) expense | (30) | 206 | (10) | 1 | (10) |
| Net loss | $ (15,559) | $ (7,602) | $ (17,408) | $ (2,247) | $ (7,229) |
| Net loss per share, basic and diluted[(1)] | | $ (85.82) | $ (2.12) | $ (13.06) | $ (0.20) |
| Shares used to compute basic and diluted net loss per share[(1)] | | 88,582 | 8,212,538 | 171,998 | 35,872,606 |

*(1) See Note 2 of our Notes to Financial Statements incorporated by reference in this prospectus for an explanation of the method used to calculate the basic and diluted net loss per common share and the number of shares used in the computation of the share and per share data. No share or per share data have been presented for 2010 since we had no common shares outstanding during that year.*

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The unaudited as adjusted balance sheet data set forth below give effect to our issuance and sale of 4,500,000 shares of our common stock in this offering at the public offering price of $9.50 per share, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

| | As of March 31, 2013 | |
|---|---|---|
| **Balance sheet data** | **Actual** | **Pro forma as adjusted** |
| | **(unaudited, in thousands)** | |
| Cash, cash equivalents and short-term investments | $ 90,715 | $ 130,540 |
| Working capital | 79,076 | 118,901 |
| Total assets | 97,027 | 136,852 |
| Convertible notes payable | 11,895 | 11,895 |
| Accumulated deficit | (67,648) | (67,648) |
| Total stockholders equity | 55,867 | 95,692 |

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# Risk factors

*A purchase of shares of our common stock is an investment in our securities and involves a high degree of risk. You should carefully consider the risks and uncertainties and all other information contained in or incorporated by reference in this prospectus, including the risks and uncertainties discussed under Risk Factors 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. All of these risk factors are incorporated by reference herein in their entirety. If any of these risks actually occur, our business, financial condition and results of operations would likely suffer. In that case, the market price of our common stock could decline, and you may lose part or all of your investment in our company. Additional risks of which we are not presently aware or that we currently believe are immaterial may also harm our business and results of operations.*

**RISKS RELATED TO THIS OFFERING AND OWNERSHIP OF OUR COMMON STOCK**

**The market price of our common stock may be highly volatile, and you may not be able to resell your shares at or above the public offering price.**

The trading price of our common stock is likely to continue to be volatile. Since shares of our common stock were sold in our initial public offering in October 2012 at a price of $4.00 per share, our closing stock price as reported on The NASDAQ Global Market has ranged from $4.15 to $12.41, through July 16, 2013.

Our stock price could be subject to wide fluctuations in response to a variety of factors, including the following:

- adverse results or delays in preclinical testing or clinical trials;
- inability to obtain additional funding;
- any delay in filing an IND or NDA for any of our future product candidates and any adverse development or perceived adverse development with respect to the FDA s review of that IND or NDA;
- failure to maintain our existing strategic alliances or enter into new alliances;
- failure of our strategic alliance partners to elect to develop and commercialize product candidates under our alliance agreements or the termination of any programs under our alliance agreements;
- failure by us or our licensors and strategic alliance partners to prosecute, maintain or enforce our intellectual property rights;
- failure to successfully develop and commercialize our future product candidates;

- changes in laws or regulations applicable to our preclinical and clinical development activities, product candidates or future products;
- inability to obtain adequate product supply for our future product candidates or the inability to do so at acceptable prices;
- adverse regulatory decisions;
- introduction of new products, services or technologies by our competitors;
- failure to meet or exceed financial projections we may provide to the public;
- failure to meet or exceed the estimates and projections of the investment community;

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**Risk factors**

- Ø the perception of the pharmaceutical industry by the public, legislatures, regulators and the investment community;
- Ø announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us, our strategic alliance partners or our competitors;
- Ø disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- Ø additions or departures of key scientific or management personnel;
- Ø significant lawsuits, including patent or stockholder litigation;
- Ø changes in the market valuations of similar companies;
- Ø sales of our common stock by us or our stockholders in the future; and
- Ø trading volume of our common stock.

In addition, companies trading in the stock market in general, and The NASDAQ Global Market in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance.

**Our principal stockholders and management own a significant percentage of our stock and will be able to exert significant control over matters subject to stockholder approval.**

Our executive officers, directors, 5% stockholders and their affiliates beneficially own approximately 80% of our voting stock before this offering and, upon closing of this offering, that same group will beneficially own approximately 72% of our outstanding voting stock. Therefore, even after this offering, these stockholders will have the ability to influence us through this ownership position. These stockholders may be able to determine all matters requiring stockholder approval. For example, these stockholders, acting together, may be able to control elections of directors, amendments of our organizational documents, or approval of any merger, sale of assets, or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may believe are in your best interest as one of our stockholders.

**Even if this offering is successful, we may need to raise additional funding, which may not be available on acceptable terms, or at all.**

Developing pharmaceutical products, including conducting preclinical studies and clinical trials, is expensive. We expect our research and development expenses to substantially increase in connection with our ongoing activities, particularly as we advance our product candidates toward clinical programs. If we are unable to successfully complete this offering, we will need to seek alternative financing or change our operational plans to continue as a going concern. 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.

We estimate that the net proceeds from this offering will be approximately $39.8 million. We expect that the net proceeds from this offering and our existing cash and cash equivalents, together with interest, will be sufficient to fund our current operations through at least the end of 2016. However, changing circumstances may cause us to consume capital more rapidly than we currently anticipate. For example, as we move our lead compounds through toxicology and other preclinical studies, also referred to as

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**Risk factors**

nonclinical studies, required to file an investigational new drug application, or IND, and as we conduct clinical development of RG-101 and any other future product candidates, we may have adverse results requiring that we find new product candidates. Additionally, our strategic alliance partners may not elect to pursue the development and commercialization of any of our *micro*RNA product candidates that are subject to their respective strategic alliance agreements with us. Any of these events may increase our development costs more than we expect. We may need to raise additional funds or otherwise obtain funding through strategic alliances if we choose to initiate clinical trials for new product candidates other than programs currently partnered. In any event, we will require additional capital to obtain regulatory approval for, and to commercialize, future product candidates. Raising funds in the current economic environment, when the capital markets have been affected by the global recession, may present additional challenges.

If we are required to secure additional financing, such additional fundraising efforts may divert our management from our day-to-day activities, which may adversely affect our ability to develop and commercialize future product candidates. In addition, we cannot guarantee that future financing will be available in sufficient amounts or on terms acceptable to us, if at all. If we are unable to raise additional capital when required or on acceptable terms, we may be required to:

- Ø significantly delay, scale back or discontinue the development or commercialization of any future product candidates;
- Ø seek strategic alliances for research and development programs at an earlier stage than otherwise would be desirable or on terms that are less favorable than might otherwise be available; or
- Ø relinquish or license on unfavorable terms, our rights to technologies or any future product candidates that we otherwise would seek to develop or commercialize ourselves.

If we are required to conduct additional fundraising activities and we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we will be prevented from pursuing development and commercialization efforts, which will have a material adverse effect on our business, operating results and prospects.

**We are an emerging growth company, and we cannot be certain if the reduced reporting requirements applicable to emerging growth companies will make our common stock less attractive to investors.**

We are an emerging growth company, as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. For as long as we continue to be an emerging growth company, we may take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies, including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, reduced disclosure obligations regarding executive compensation in this prospectus and our periodic reports and proxy statements and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved. We could be an emerging growth company through December 31, 2017, although circumstances could cause us to lose that status earlier, including if the market value of our common stock held by non-affiliates exceeds $700.0 million as of any June 30 before that time or if we have total annual gross revenue of $1.0 billion or more during any fiscal year before that time, in which cases we would no longer be an emerging growth company as of the following December 31 or, if we issue more than $1.0 billion in non-convertible debt during any three year period before that time, we would cease to be an emerging growth company immediately. Even after we no longer qualify as an emerging growth company, we may still qualify as a smaller reporting company which would allow us to take

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advantage of many of the same exemptions from disclosure requirements including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act and reduced disclosure obligations regarding executive compensation in this prospectus and our periodic reports and proxy statements. We cannot predict if investors will find our common stock less attractive because we may rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

Under the JOBS Act, emerging growth companies can also delay adopting new or revised accounting standards until such time as those standards apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

**Sales of a substantial number of shares of our common stock in the public market by our existing stockholders could cause our stock price to fall.**

Sales of a substantial number of shares of our common stock in the public market or the perception that these sales might occur could depress the market price of our common stock and could impair our ability to raise capital through the sale of additional equity securities. We are unable to predict the effect that sales may have on the prevailing market price of our common stock.

We, along with our directors and executive management team have agreed that for a period of 90 days after the date of this prospectus, subject to specified exceptions, we or they will not offer, sell, contract to sell, pledge or otherwise dispose of, directly or indirectly, any shares of our common stock or securities convertible into or exchangeable or exercisable for any shares of our common stock. Subject to certain limitations, approximately 140,327 shares will become eligible for sale upon expiration of such lock-up period, as calculated and described in more detail in the section entitled Shares eligible for future sale. In addition, shares issued or issuable upon exercise of options vested as of the expiration of the lock-up period will be eligible for sale at that time. Sales of stock by these stockholders could have a material adverse effect on the trading price of our common stock.

An additional 26,515,110 shares of our common stock are subject to lock-up agreements that were entered into in connection with our initial public offering, which lock-up agreements expire on October 4, 2013.

Certain holders of our securities are entitled to rights with respect to the registration of their shares under the Securities Act of 1933, as amended, or the Securities Act, subject to the applicable lock-up arrangement described above. Registration of these shares under the Securities Act would result in the shares becoming freely tradable without restriction under the Securities Act, except for shares held by our affiliates as defined in Rule 144 under the Securities Act. Any sales of securities by these stockholders could have a material adverse effect on the trading price of our common stock.

**Future sales and issuances of our common stock or rights to purchase common stock, including pursuant to our equity incentive plans, could result in additional dilution of the percentage ownership of our stockholders and could cause our stock price to fall.**

We expect that significant additional capital will be needed in the future to continue our planned operations. To the extent we raise additional capital by issuing equity securities, our stockholders may experience substantial dilution. We may sell common stock, convertible securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell common stock, convertible securities or other equity securities in more than one transaction, investors may be materially diluted by subsequent sales. These sales may also result in material dilution to our existing stockholders, and new investors could gain rights superior to our existing stockholders.

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Pursuant to our 2012 equity incentive plan, or the 2012 Plan, our management is authorized to grant stock options and other equity-based awards to our employees, directors and consultants. The number of shares available for future grant under the 2012 Plan will automatically increase each year by up to 4% of all shares of our capital stock outstanding as of December 31 of the prior calendar year, subject to the ability of our board of directors to take action to reduce the size of the increase in any given year. Any such increase, of the maximum amount or a lesser amount, will cause our stockholders to experience additional dilution, which could cause our stock price to fall. Currently, we plan to register the increased number of shares available for issuance under the 2012 Plan each year.

**We have broad discretion in the use of the net proceeds from this offering and may not use them effectively.**

Our management will have broad discretion in the application of the net proceeds 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. The failure by our management to apply these funds effectively could harm our business. Pending their use, we may invest the net proceeds from this offering in short-term, investment-grade, interest-bearing securities. These investments may not yield a favorable return to our stockholders.

**Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited.**

Under Section 382 of the Internal Revenue Code of 1986, as amended, if a corporation undergoes an ownership change, generally defined as a greater than 50% change (by value) in its equity ownership over a three year period, the corporation s ability to use its pre-change net operating loss carryforwards, or NOLs, and other pre-change tax attributes (such as research tax credits) to offset its post-change income may be limited. We believe that, with our initial public offering and other transactions that have occurred over the past three years, we may have triggered an ownership change limitation. We may also experience ownership changes in the future as a result of subsequent shifts in our stock ownership. As a result, if we earn net taxable income, our ability to use our pre-change net operating loss carryforwards to offset U.S. federal taxable income may be subject to limitations, which could potentially result in increased future tax liability to us. In addition, at the state level, there may be periods during which the use of NOLs is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed.

**We do not intend to pay dividends on our common stock so any returns will be limited to the value of our stock.**

We have never declared or paid any cash dividends on our common stock. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Any return to stockholders will therefore be limited to the appreciation of their stock.

**RISKS RELATED TO OUR INTELLECTUAL PROPERTY**

**Third-party claims of intellectual property infringement may prevent or delay our development and commercialization efforts.**

Our commercial success depends in part on our avoiding infringement of the patents and proprietary rights of third parties. There is a substantial amount of litigation, both within and outside the United States,

**Risk factors**

involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, interferences, oppositions and inter partes reexamination proceedings before the U.S. Patent and Trademark Office and corresponding foreign patent offices. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we and our strategic alliance partners are pursuing development candidates. For example, we are aware that Santaris Pharma A/S, or Santaris, has patents and patent applications in the *micro*RNA therapeutics space, including patents and patent applications related to targeting *micro*RNAs, such as miR-122, for the treatment of disease. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our future product candidates may be subject to claims of infringement of the patent rights of third parties.

Third parties may assert that we are employing their proprietary technology without authorization. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our future product candidates. Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in issued patents that our future product candidates may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. If any third-party patents were held by a court of competent jurisdiction to cover the manufacturing process of any of our future product candidates, any molecules formed during the manufacturing process or any final product itself, the holders of any such patents may be able to block our ability to commercialize such product candidate unless we obtained a license under the applicable patents, or until such patents expire. Similarly, if any third-party patents were held by a court of competent jurisdiction to cover aspects of our formulations, processes for manufacture or methods of use, including combination therapy, the holders of any such patents may be able to block our ability to develop and commercialize the applicable product candidate unless we obtained a license or until such patent expires. In either case, such a license may not be available on commercially reasonable terms or at all.

Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our future product candidates. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys fees for willful infringement, pay royalties, redesign our infringing products or obtain one or more licenses from third parties, which may be impossible or require substantial time and monetary expenditure.

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# Special note regarding forward-looking statements

This prospectus contains forward-looking statements. The forward-looking statements are contained principally in the sections entitled Prospectus summary, Risk factors, Management s discussion and analysis of financial condition and results of operations and Business in this prospectus or incorporated by reference herein. These statements relate to future events or to our future financial performance and involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. Forward-looking statements include, but are not limited to, statements about:

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

- regulatory developments in the United States and foreign countries;
- the performance of our third-party suppliers and manufacturers;
- the success of competing therapies that are or become available;
- the loss of key scientific or management personnel;
- our expectations regarding the time during which we will be an emerging growth company under the JOBS Act;
- our use of the proceeds from this offering; and
- the accuracy of our estimates regarding expenses, future revenues, capital requirements and need for additional financing.

In some cases, you can identify these statements by terms such as anticipate, believe, could, estimate, expect, intend, may, plan, p predict, project, should, will, would or the negative of those terms, and similar expressions. These forward-looking statements reflect our management s beliefs and views with respect to future events and are based on estimates and assumptions as of the date of this prospectus and are subject to risks and uncertainties. We discuss many of these risks in greater detail under the heading Risk factors. Moreover, we operate in a very

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**Special note regarding forward-looking statements**

competitive and rapidly changing environment. New risks emerge from time to time. It is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements we may make. Given these uncertainties, you should not place undue reliance on these forward-looking statements. The Private Securities Litigation Reform Act of 1995 and Section 27A of the Securities Act of 1933, as amended, do not protect any forward-looking statements that we make in connection with this offering.

You should read this prospectus and the documents that we reference in this prospectus and have filed as exhibits to the registration statement, of which this prospectus is a part, completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of the forward-looking statements in this prospectus by these cautionary statements.

Except as required by law, we assume no obligation to update these forward-looking statements publicly, or to update the reasons actual results could differ materially from those anticipated in these forward-looking statements, even if new information becomes available in the future.

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# Use of proceeds

We estimate that we will receive net proceeds of approximately $39.8 million (or approximately $45.9 million if the underwriters over-allotment option is exercised in full) from the sale of the shares of common stock offered by us in this offering, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

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 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 *micro*RNA 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 that we may use for the purposes specified above. Accordingly, we will have broad discretion in the use of the net proceeds from this offering and could spend the proceeds in ways that do not improve our results of operations or enhance the value of our stock. 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.

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# Price range of our common stock

Our common stock has been listed on the NASDAQ Global Market since October 4, 2012 under the symbol RGLS . Prior to that date, there was no public market for our common stock. Shares sold in our initial public offering on October 4, 2012 were priced at $4.00 per share.

On July 16, 2013, the closing price for our common stock as reported on the NASDAQ Global Market was $10.69 per share. The following table sets forth the ranges of high and low sales prices per share of our common stock as reported on the NASDAQ Global Market for the period indicated. Such quotations represent inter-dealer prices without retail markup, markdown or commission and may not necessarily represent actual transactions.

| **Year Ended December 31, 2012** | **High** | **Low** |
|---|---|---|
| Fourth Quarter (from October 4, 2012) | $6.49 | $4.02 |
| **Year Ended December 31, 2013** | **High** | **Low** |
| First Quarter | $7.89 | $4.67 |
| Second Quarter | $10.94 | $6.44 |
| Third Quarter (through July 16, 2013) | $12.89 | $9.78 |

As of July 16, 2013, there were 17 stockholders of record, which excludes stockholders whose shares were held in nominee or street name by brokers. The actual number of common stockholders is greater than the number of record holders, and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers and other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

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# Equity compensation plan information

The following table provides certain information with respect to all of our equity compensation plans in effect as of December 31, 2012:

| Plan Category | Number of securities to be issued upon exercise of outstanding options, restricted stock units and rights (a) | Weighted-average exercise price of outstanding options (b) | Number of securities remaining available for issuance under equity compensation plans (excluding securities reflected in column (a)) (c) |
|---|---|---|---|
| Equity compensation plans approved by security holders[1] | 4,719,799 | $ 2.11 | 1,485,711 |
| Equity compensation plans not approved by security holders | | | |
| Total | 4,719,799 | $ 2.11 | 1,485,711 |

*(1) Available for the grant of future rights under our 2012 equity incentive plan, or 2012 Plan, and 2012 employee stock purchase plan, or ESPP, as of December 31, 2012, excluding future increases in the number of shares of common stock reserved for issuance under the 2012 Plan and ESPP pursuant to the evergreen provisions therein.*

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# Dividend policy

We have never declared or paid any cash dividends on our common stock. We currently intend to retain all available funds and any future earnings to support our operations and finance the growth and development of our business. We do not intend to pay cash dividends on our common stock for the foreseeable future. Any future determination related to our dividend policy will be made at the discretion of our board of directors and will depend upon, among other factors, our results of operations, financial condition, capital requirements, contractual restrictions, business prospects and other factors our board of directors may deem relevant.

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# Capitalization

The following table sets forth our cash, cash equivalents and short-term investments, and our capitalization as of March 31, 2013:

Ø on an actual basis;

Ø on a pro forma as adjusted basis to reflect the sale by us of 4,500,000 shares of our common stock in the offering at the public offering price of $9.50 per share, after deducting the underwriting discounts and commissions and estimated offering costs payable by us.

You should read this table together with Management s discussion and analysis of financial condition and results of operations and our financial statements and the related notes appearing elsewhere in this prospectus or incorporated by reference herein.

| | As of March 31, 2013 | |
|---|---|---|
| | Actual | Pro forma as adjusted |
| | (unaudited, in thousands, except share and per share data) | |
| Cash, cash equivalents and short-term investments | $ 90,715 | $ 130,540 |
| Convertible notes payable[1] | 11,895 | 11,895 |
| Convertible preferred stock; $0.001 par value: 10,000,000 shares authorized, no shares issued or outstanding, actual; 10,000,000 shares authorized, no shares issued or outstanding, pro forma as adjusted | | |
| Stockholders equity: | | |
| Common stock; $0.001 par value: 200,000,000 shares authorized, 35,965,371 shares issued and outstanding, actual; 200,000,000 shares authorized and 40,465,371 shares issued and outstanding, pro forma as adjusted | 36 | 40 |
| Additional paid-in capital | 123,516 | 163,337 |
| Accumulated other comprehensive loss | (37) | (37) |
| Accumulated deficit | (67,648) | (67,648) |
| Total stockholders equity | 55,867 | 95,692 |
| Total capitalization | $ 67,762 | $ 107,587 |

*(1) In October 2012, in conjunction with our initial public offering, the promissory note we issued to Glaxo Group Limited, or GSK, in 2010 was amended and restated with a principal amount of $5.4 million. This amended note had a maturity date of three years from the anniversary of the agreement, or October 2015. At GSK s option, this note shall be convertible into shares of our common stock at any time prior to the maturity date with a conversion equal to the quotient of all outstanding principal and interest divided by the initial public offering price of $4.00 per share. The value attributed to the convertible note*

*payable in the table above reflects the fair value of the note, including the conversion option. The outstanding principal of the convertible note payable as of March 31, 2013 was $5.4 million, which would result in total capitalization of $101.1 million on a pro forma as adjusted basis.*

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**Capitalization**

The number of shares of common stock shown as issued and outstanding on a pro forma as adjusted basis in the table is based on the number of shares of our 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.

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# Dilution

If you invest in our common stock in this offering, your ownership interest will be immediately diluted to the extent of the difference between the public offering price per share and the pro forma as adjusted net tangible book value per share of our common stock after this offering.

Our historical net tangible book value per share is determined by dividing our total tangible assets less total liabilities by the actual number of outstanding shares of our common stock. The historical net tangible book value of our common stock as of March 31, 2013 was $54.7 million, or $1.52 per share.

After giving effect to the sale of 4,500,000 shares of our common stock offered by us at the public offering price of $9.50 per share, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us, our net tangible book value as of March 31, 2013, would have been approximately $94.5 million, or $2.34 per share of common stock. This represents an immediate increase in net tangible book value of $0.82 per share to existing stockholders and an immediate dilution of $7.16 per share to new investors purchasing shares of common stock in this offering at the public offering price.

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

| | | |
|---|---|---|
| Offering price per share | | $ 9.50 |
| Historical net tangible book value per share as of March 31, 2013 | $ 1.52 | |
| Increase in net tangible book value per share attributable to new investors | 0.82 | |
| Pro forma as adjusted net tangible book value per share after the offering | | 2.34 |
| Dilution per share to new investors | | $ 7.16 |

If the underwriters exercise in full their option to purchase up to 675,000 additional shares of common stock at the public offering price of $9.50 per share, the as adjusted net tangible book value after this offering would be $100.5 million, or $2.44 per share, representing an increase in net tangible book value of $0.92 per share to existing stockholders and immediate dilution in net tangible book value of $7.06 per share to investors purchasing our common stock in this offering at the public offering price.

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**Dilution**

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.

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# Selected financial data

The following selected financial data should be read together with our financial statements and accompanying notes and Management s discussion and analysis of financial condition and results of operations appearing elsewhere in this prospectus or incorporated by reference herein. The selected financial data in this section are not intended to replace our financial statements and the related notes. Our historical results are not necessarily indicative of our future results.

The selected statement of operations data for the years ended December 31, 2010, 2011 and 2012 and the selected balance sheet data as of December 31, 2011 and 2012 are derived from our audited financial statements incorporated by reference in this prospectus. The selected statement of operations data for the three months ended March 31, 2012 and 2013 and the selected balance sheet data as of March 31, 2013 are derived from our unaudited financial statements incorporated by reference in this prospectus. The unaudited financial statements have been prepared on a basis consistent with our audited financial statements included in this prospectus and include, in our opinion, all adjustments, consisting of normal recurring adjustments necessary for the fair presentation of the financial information in those statements.

| | 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 | $ 8,112 | $ 13,767 | $ 12,700 | $ 3,344 | $ 3,238 |
| Grant revenue | 489 | 22 | | | |
| Total revenues | 8,601 | 13,789 | 12,700 | 3,344 | 3,238 |
| Operating expenses: | | | | | |
| Research and development | 20,178 | 17,289 | 20,342 | 4,603 | 6,883 |
| General and administrative | 3,921 | 3,637 | 4,932 | 921 | 1,905 |
| Total operating expenses | 24,099 | 20,926 | 25,274 | 5,524 | 8,788 |
| Loss from operations | (15,498) | (7,137) | (12,574) | (2,180) | (5,550) |
| Other expense, net | (91) | (259) | (4,844) | (66) | (1,689) |
| Loss before income taxes | (15,589) | (7,396) | (17,418) | (2,246) | (7,239) |
| Income tax (benefit) expense | (30) | 206 | (10) | 1 | (10) |
| Net loss | $ (15,559) | $ (7,602) | $ (17,408) | $ (2,247) | $ (7,229) |
| Net loss per share, basic and diluted[(1)] | | $ (85.82) | $ (2.12) | $ (13.06) | $ (0.20) |
| Shares used to compute basic and diluted net loss per share[(1)] | | 88,582 | 8,212,538 | 171,998 | 35,872,606 |

*(1)*

*See Note 2 of our Notes to Financial Statements incorporated by reference in this prospectus for an explanation of the method used to calculate the basic and diluted net loss per common share and the number of shares used in the computation of the share and per share data. No share or per share data have been presented for 2010 since we had no common shares outstanding during that year.*

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**Selected financial data**

| Balance sheet data | As of December 31, 2011 | 2012 | As of March 31, 2013 (unaudited) |
|---|---|---|---|
| | | (in thousands) | |
| Cash, cash equivalents and short-term investments | $ 38,144 | $ 98,100 | $ 90,715 |
| Working capital | 25,816 | 86,161 | 79,076 |
| Total assets | 42,881 | 103,518 | 97,027 |
| Convertible notes payable | 10,815 | 10,134 | 11,895 |
| Accumulated deficit | (43,011) | (60,419) | (67,648) |
| Total stockholders (deficit) equity | (41,494) | 62,093 | 55,867 |

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# Business

## OVERVIEW

### Our business

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. *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 lnc. to evaluate the potential use of *micro*RNA signatures as a biomarker for human patients with multiple sclerosis.

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 toward 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 as 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 investigation new drug 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 candidate by the end of 2013.

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 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. This provided the foundation for our leadership position in the *micro*RNA field and, since then, we have leveraged their RNA-based discovery and development expertise, established over more than 20 years, to build our own proprietary *micro*RNA product platform that combines a deep understanding of biology with innovative chemistries and disciplined processes.

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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 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, or overproduced, 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 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 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 a letter agreement pursuant to which we granted Sanofi an exclusive right to negotiate for the co-development and commercialization of certain of our unencumbered *micro*RNA programs through December 2013, for which Sanofi has paid 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.

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Under our existing strategic alliances with AstraZeneca, GSK and Sanofi, we are eligible to receive up to approximately $1.3 billion in milestone payments upon successful commercialization of *micro*RNA therapeutics for the eight 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.

**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. Hoffman-La Roche Inc. in 2011), which he started as President and Chief Executive Officer.

- 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:

Ø 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.

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- 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.

**THE 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. This is achieved when the *micro*RNA binds with its messenger RNA targets and blocks cell machinery, called ribosomes, from translating them into proteins, as shown below.

Step 1. *micro*RNAs are transcribed from DNA in the nucleus and exported to the cytoplasm.

Step 2. In the cytoplasm, *micro*RNAs associate with the RNA-induced silencing complex, or RISC.

Step 3. The *micro*RNA in RISC targets specific messenger RNAs.

Step 4. The *micro*RNA interaction with its target messenger RNAs blocks translation into proteins.

RNA therapeutics are drugs designed to specifically target RNA. The field of RNA therapeutics consists of various technologies including antisense therapeutics, RNAi therapeutics and *micro*RNA therapeutics:

*Antisense therapeutics* Antisense therapeutics are small oligonucleotides that target RNA through hybridization, a specific type of binding, and modulate the function of the targeted RNA. There are at least 12 known antisense mechanisms that can be exploited once an antisense drug binds to its target RNA. One of our founding companies, Isis, is leading the discovery and development of antisense therapeutics with over 25 drugs currently in development. Isis most advanced drug, KYNAMRO ,

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which is partnered with Genzyme Corporation, a subsidiary of Sanofi, was approved by the FDA in January 2013 for the treatment of homozygous familial hypercholesterolemia. The majority of Isis antisense drugs in development bind to the specific RNAs of a particular gene, and ultimately inhibit or alter the expression of the protein encoded in the target gene.

*RNAi therapeutics* RNAi therapeutics are RNA-like oligonucleotides that harness RNAi, a powerful and natural biologic mechanism that was awarded the 2006 Nobel Prize for Physiology or Medicine. RNAi therapeutics are rationally designed to silence disease causing genes. The molecule that mediates RNAi, small interfering RNA, or siRNA, binds with a cellular complex known as the RNA-induced silencing complex, or RISC. The siRNA within RISC is processed into single-stranded RNA that targets a specific messenger RNA and promotes its degradation through cleavage. In this way, RNAi therapeutics can be used to target specific disease causing genes. One of our founding companies, Alnylam, has shown human proof-of-concept in clinical trials with multiple RNAi drug candidates.

*microRNA therapeutics* *micro*RNA therapeutics are single- or double-stranded RNA-like oligonucleotides that are chemically modified and target specific *micro*RNAs. Single-stranded *micro*RNA therapeutics, or anti-miRs, are designed to bind and inhibit specific *micro*RNAs that have been up-regulated in diseases as shown in the figure below. Double-stranded *micro*RNA therapeutics, or miR-mimics, are designed to replace the activity of specific *micro*RNAs that have been down-regulated in disease. In this way, *micro*RNA therapeutics can be used to modulate specific *micro*RNA targets and regulate entire biological pathways.

Step 1. *micro*RNA expression is up-regulated in disease such that a specific *micro*RNA is produced in excess amounts.

Step 2. The up-regulated *micro*RNA targets messenger RNAs, resulting in lower levels of key proteins.

Step 3. The anti-miR therapeutic is delivered to the diseased cell and binds to the up-regulated *micro*RNA, resulting in the elimination of excess *micro*RNA.

Step 4. Use of the anti-miR therapeutic therefore restores the normal function of *micro*RNA biology in the cell and corrects the disease.

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***micro*RNA THERAPEUTICS AS A NEW CLASS OF DRUGS**

We believe that *micro*RNA therapeutics have the potential to become a new and major class of drugs with broad therapeutic application. There are several reasons why *micro*RNA therapeutics have transformative potential, some of which are listed below.

*microRNAs represent a new drug target space* *micro*RNAs are a recent discovery in biology and, up until now, have not been a focus of pharmaceutical research. Traditional drug classes cannot be used to target *micro*RNAs because they are typically designed to bind and inhibit proteins, not RNA molecules. *micro*RNA therapeutics provide the capability to very specifically modulate *micro*RNAs and allow access to this new target space.

*microRNAs are dysregulated in a broad range of diseases* *micro*RNAs play a critical role in regulating biological pathways by controlling the translation of many target genes. More than 500 *micro*RNAs have been identified to date in humans, each of which are believed to interact with a specific set of genes that control key aspects of cell biology. Thus the improper balance, or dysregulation, of *micro*RNAs has been directly linked to numerous diseases, including cancer, diabetes, congestive heart failure, viral infections and macular degeneration.

*microRNA therapeutics target entire disease pathways* *micro*RNAs are naturally occurring molecules that have evolved to regulate gene networks responsible for entire biological pathways. Because of this unique attribute, the use of *micro*RNA therapeutics may allow for more effective treatment of complex multi-factorial diseases in which the entire disease pathway can be addressed.

*microRNA therapeutics can be produced with efficient rational design* Traditional drug classes, like small molecules, usually require screening of thousands of potential compounds to identify prospective leads. Given that *micro*RNAs are a short sequence of nucleotides and that the corresponding sequence of the mirror image anti-miR is also known, *micro*RNA therapeutics allow for a more efficient rational drug design process.

*microRNA therapeutics may be synergistic with other therapies* Because of their completely different mechanisms of action, *micro*RNA therapeutics and traditional drugs can be synergistic. In certain fields, such as cancer and infectious diseases, physicians typically treat patients with combinations of drugs that have different mechanisms in the hope that there will be complementary activity.

**OUR *micro*RNA PRODUCT PLATFORM**

We are the leading company in the field of *micro*RNA therapeutics dedicated to pioneering a new paradigm in treating serious diseases. We believe we have assembled the leading position in the *micro*RNA field, including expertise in *micro*RNA biology and oligonucleotide chemistry, 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. 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 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, including the first researcher to discover *micro*RNAs in humans;

-

access to proven RNA therapeutic technologies through our founding companies, as well as approximately 900 patents and patent applications relating to oligonucleotide technologies;

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

- 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 to the discovery and development of *micro*RNA therapeutics is as important as the assets assembled to execute on our plans. Beginning with how we evaluate a therapeutic opportunity and followed by the identification of a specific *micro*RNA target, its validation and optimization of the development candidates that will go into clinical trials, each is the subject of proprietary standards and rules that increase our probability of technical success. Our disciplined approach 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.

The advantage of our evaluation criteria is that they can be applied to a broad range of *micro*RNA targets, allowing us to generate a focused portfolio of discovery programs that we believe have a high probability of clinical and commercial success.

Once we have decided to initiate a new program, we use a disciplined approach to identify novel *micro*RNA targets, validate such novel *micro*RNA targets and use our proprietary methodologies to optimize lead *micro*RNA development candidates for IND-enabling studies and subsequent clinical development.

*Step 2 - Identification of microRNA targets*

We have developed a significant understanding and know-how of human *micro*RNA biology and the biological pathways that are regulated by *micro*RNAs. 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 diseases 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 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 diseases and not simply correlating markers.

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*Step 4 - Optimization of microRNA development candidates*

We have developed a proprietary process that allows us to rapidly generate an optimized development candidate following the identification and validation of a *micro*RNA target. 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 that quickly allow us to:

- identify our most effective anti-miRs in mechanistic cell-based assays;
- evaluate the activity of our anti-miRs in preclinical animal models that are predictive of human diseases; and
- eliminate anti-miRs that may trigger undesirable effects.

We also enhance our anti-miRs for distribution to the tissues where the specific *micro*RNA target is causing disease. For example, we employ a conjugate approach to successfully deliver anti-miRs to target tissues and achieve optimized cellular uptake. Our conjugate platform includes several receptor-mediated chemistries such as triantennary N-acetylgalactosamine, or GalNAc, conjugates. We have demonstrated the ability to achieve optimized delivery to cells in the liver with both intravenous and subcutaneous administration of GalNAc conjugates in multiple species and with multiple targets.

We believe that our optimization process provides us with a competitive advantage in the discovery and development of *micro*RNA therapeutics. The lessons we learn from one program can be applied to other programs at an earlier stage in our portfolio, leading to potential acceleration of the advancement of those programs towards IND-enabling activities and future clinical development.

***micro*RNA BIOMARKERS**

Through our *micro*RNA target identification and validation efforts we have developed proprietary technologies for *micro*RNA profiling and analysis of human clinical samples such as tissue biopsies. More recently, *micro*RNAs have been detected in bodily fluids such as blood, and emerging data generated by us and others have demonstrated that *micro*RNA signatures in blood can mimic the expression profile observed in disease tissues.

The identification of dysregulated *micro*RNAs from various human tissues and blood helps us identify and validate potential *micro*RNA targets for therapeutic development. Equally important, such *micro*RNAs may become biomarkers that can be used to select optimal patient segments for our clinical trials. We expect this personalized approach to clinical development to result in a significantly improved risk-benefit ratio in the appropriate patient populations and plan to implement the strategy in our programs.

We believe that *micro*RNA biomarkers in the blood are of significant value and provide opportunities to develop companion diagnostics for any drugs that we may successfully develop and drugs developed by other companies. In August 2012, we entered into an agreement with Biogen Idec MA Inc. to collaborate on *micro*RNA biomarkers for multiple sclerosis.

**OUR INITIAL DEVELOPMENT CANDIDATES**

We have demonstrated in at least 20 preclinical animal models that are predictive of human diseases that the inhibition of up-regulated *micro*RNA targets using anti-miRs can modulate entire biological pathways, returning diseased cells to their healthy state. Based on the

extensive preclinical data we have

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generated to date, we believe that our *micro*RNA product platform has the potential to provide significant therapeutic benefit in a broad range of human diseases. We have chosen to focus our initial efforts on select therapeutic areas with unmet medical needs including HCV, oncology and metabolic diseases. We have identified and validated several *micro*RNA targets that play a role in these areas.

Our *micro*RNA development candidates target miR-122 in HCV, miR-21 and miR-221 in hepatocellular carcinoma, miR-21 in kidney fibrosis, miR-33 in atherosclerosis and miR-10b in GBM.

**RG-101 targeting miR-122 in hepatitis C virus infection**

*Market opportunity:*

Hepatitis C is a result of a hepatocyte specific infection induced by the virus known as HCV. Chronic HCV may lead to significant liver disease, including chronic active hepatitis, cirrhosis, and hepatocellular carcinoma. According to the World Health Organization, up to 170 million people are chronically infected with HCV worldwide, and more than 350,000 people die from HCV annually. The CDC estimates that there are currently approximately 3.2 million persons infected with HCV in the United States.