Regulus Therapeutics Inc.
Form 10-K
February 19, 2013
Table of Contents

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, DC 20549

Form 10-K

(Mark One)

x **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2012

or

¨ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from to

Commission file number: 001-35670

Regulus Therapeutics Inc.

(Exact Name of Registrant as Specified in its Charter)

Delaware	26-4738379
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)
3545 John Hopkins Ct., Suite 210, San Diego CA	92121
(Address of Principal Executive Offices)	(Zip Code)

(858) 202-6300

(Registrant s Telephone Number, Including Area Code)

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	Name of Each Exchange on Which Registered
Common Stock, par value $0.001 per share	The NASDAQ Stock Market LLC

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ¨ No x

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. Yes ¨ No x

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes x No ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes x No ¨

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of the registrant s knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ¨

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

Large accelerated filer ¨ Accelerated filer ¨ Non-accelerated filer ¨ Smaller reporting company x
Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Securities Exchange Act of 1934). Yes ¨ No x

The registrant did not have a public float on the last business day of its most recently completed second fiscal quarter because there was no public market for the registrant s common equity as of such date.

The number of outstanding shares of the registrant s common stock, par value $0.001 per share, as of February 14, 2013 was 35,883,058.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant s proxy statement to be filed with the Securities and Exchange Commission pursuant to Regulation 14A in connection with the registrant s 2013 Annual Meeting of Stockholders, which will be filed subsequent to the date hereof, are incorporated by reference into Part III of this Form 10-K. Such proxy statement will be filed with the Securities and Exchange Commission not later than 120 days following the end of the registrant s fiscal year ended December 31, 2012.

Table of Contents

Regulus Therapeutics Inc.

FORM 10-K

For the Fiscal Year Ended December 31, 2012

Table of Contents

Table of Contents

PART I

Forward-Looking Statements

This Annual Report on Form 10-K. or this Annual Report, may contain forward-looking statements within the meaning of the federal securities laws made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Our actual results could differ materially from those anticipated in these forward-looking statements as a result of various factors, including those set forth below under Part I, Item 1A, Risk Factors in this Annual Report. Except as required by law, we assume no obligation to update these forward-looking statements, whether as a result of new information, future events or otherwise. These statements, which represent our current expectations or beliefs concerning various future events, may contain words such as may, will, expect, anticipate, intend, plan, believe, estimate or other w indicating future results. Such statements may include, but are not limited to, statements concerning the following:

- the initiation, cost, timing, progress and results of our research and development activities, preclinical studies and future clinical trials;
- our ability to obtain and maintain regulatory approval of our future product candidates, and any related restrictions, limitations, and/or warnings in the label of an approved product candidate;
- our ability to obtain funding for our operations;
- our plans to research, develop and commercialize our future product candidates;
- our strategic alliance partners election to pursue development and commercialization;
- our ability to attract collaborators with development, regulatory and commercialization expertise;
- our ability to obtain and maintain intellectual property protection for our future product candidates;
- the size and growth potential of the markets for our future product candidates, and our ability to serve those markets;
- our ability to successfully commercialize our future product candidates;
- the rate and degree of market acceptance of our future product candidates;
- 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 our recently completed initial public offering and private placement; and

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

Item 1. 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. We were formed in 2007 when Alnylam Pharmaceuticals, Inc., or Alnylam, and Isis Pharmaceuticals, Inc., or Isis, contributed significant intellectual property, know-how and

Table of Contents

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 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 five 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 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 $1.7 billion in milestone payments upon successful commercialization of *micro*RNA therapeutics for the 11 programs contemplated by our agreements. These payments include up to $106.5 million upon achievement of preclinical and investigational new drug application, or IND, milestones, up to $350.0 million upon achievement of clinical development milestones, up to $420.0 million upon achievement of regulatory milestones and up to $850.0 million upon achievement of commercialization milestones. We anticipate that we will nominate at least two clinical development candidates in 2013 and file two INDs with the U.S. Food and Drug Administration, or FDA, in 2014.

On October 10, 2012, we completed our initial public offering whereby we sold 11,250,000 shares of common stock at $4.00 per share and received net proceeds of $39.5 million (after underwriting discounts and commissions). Concurrently with the completion of our initial public offering, we sold 6,250,000 shares of common stock in a private placement to AstraZeneca at the initial public offering price of $4.00 per share and received net proceeds of $25.0 million. In addition, $5.0 million of outstanding principal plus accrued interest of $788,000 underlying a convertible note that we issued to GSK in April 2008 and amended and restated in July 2012, together with $5.0 million of outstanding principal plus accrued interest of $25,000 underlying a convertible note that we issued to Biogen Idec in August 2012, was automatically converted upon the closing of our initial public offering into an aggregate of 2,703,269 shares of our common stock. Upon the closing of our initial public offering, all 27,399,999 outstanding shares of our convertible preferred stock automatically converted into an aggregate of 13,699,999 shares of common stock. We filed an amended and restated certificate of incorporation on October 10, 2012 to authorize 200,000,000 shares of common stock and 10,000,000 shares of undesignated preferred stock. On October 23, 2012, the underwriters in our initial public offering exercised an over-allotment option to purchase 1,480,982 additional shares of our common stock at $4.00 per share, resulting in net proceeds of $5.5 million to us (after underwriting discounts).

Table of Contents

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.

Anti-miRs are designed to bind and inhibit specific *micro*RNAs that have been up-regulated in diseases as shown in the figure below:

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.

Table of Contents

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

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;
- a leading *micro*RNA intellectual property estate with access to over 1,000 patents and patent applications;
- development expertise and financial resources provided by our three major strategic alliances with AstraZeneca, GSK and Sanofi; and
- collaborations with leading academic institutions that help us identify new *micro*RNA targets.

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

Table of Contents

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.

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 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 may be easily formulated and administered systemically or locally depending on the therapeutic indication. Our five distinct therapeutic development programs are shown in the table below:

***micro*RNA target**	**anti-miR program**	**Commercial rights**
miR-21	Hepatocellular carcinoma	Sanofi
miR-21	Kidney fibrosis	Sanofi
miR-122	Hepatitis C virus infection	GlaxoSmithKline
miR-33	Atherosclerosis	AstraZeneca
miR-10b and others	Glioblastoma	Regulus

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 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 hepatitis C virus infection, or HCV.

Table of Contents

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.

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 formed a collaboration with Biogen Idec to evaluate the potential use of *mirco*RNA signatures as a biomarker for human patients with multiple sclerosis.

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 anti-miRs against several *micro*RNAs for development candidate selection. We anticipate that we will nominate at least two development candidates in 2013 and file two INDs in 2014.

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 our proprietary products in therapeutic areas such as oncology, where there are niche opportunities for development and commercialization activities that 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 microRNA 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.

Royalty Agreements

For a description of our agreements involving royalty payments, see Note 5 and Note 13 to our financial statements under Item 8 of Part II of this Annual Report.

Our Intellectual Property and Technology Licenses

Intellectual property

We strive to protect and enhance the proprietary technologies that we believe are important to our business, including seeking and maintaining patents intended to cover our products and compositions, their methods of use and any other inventions that are important to the development of our business. We also rely on trade secrets to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection.

Table of Contents

Our success will depend significantly on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business, defend and enforce our patents, preserve the confidentiality of our trade secrets and operate without infringing the valid and enforceable patents and proprietary rights of third parties. We also rely on know-how, continuing technological innovation and in-licensing opportunities to develop, strengthen and maintain our proprietary position in the field of *micro*RNA therapeutics.

We believe that we have a strong intellectual property position and substantial know-how relating to the development and commercialization of *micro*RNA therapeutics, consisting of:

- over 150 patents or patent applications that we own or have in-licensed from academic institutions and third parties including our founding companies, Alnylam and Isis, related to microRNA and microRNA drug products; and

- approximately 900 patents or patent applications exclusively licensed from our founding companies, Alnylam and Isis, related to RNA technologies, including patent and patent applications relating to chemical modification of oligonucleotides that are useful for microRNA therapeutics.

Our objective is to continue to expand our intellectual property estate through our multiple layer approach in order to protect our *micro*RNA therapeutics and to maintain our leading position in the *micro*RNA therapeutics field. Examples of the technologies covered by our patent portfolio are described below.

We have exclusively licensed patent rights from Julius-Maximilians-Universität Würzburg and Bayerische Patent Allianz GmBH, which we collectively refer to herein as the University of Würzburg, which rights encompass the use of anti-miR therapeutics targeting miR-21 for the treatment of fibrosis, including kidney, liver, lung and cardiac fibrosis. In collaboration with us, investigators at the University of Würzburg demonstrated that targeting miR-21 in a disease model resulted in beneficial phenotypic effects, including the inhibition of the development of fibrosis. The Würzburg-licensed patent portfolio includes more than 20 U.S. and foreign patents and patent applications. Any patents within this portfolio that have issued or may yet issue would have a statutory expiration date in 2029.

We and Alnylam have a co-exclusive license from Stanford University, or Stanford, to patent rights concerning the use of anti-miR therapeutics targeting miR-122 for the treatment of HCV. This patent portfolio is based upon research conducted by Peter Sarnow, Ph.D. and colleagues at Stanford, demonstrating that miR-122 is required for HCV replication in mammalian cells. The Stanford-licensed portfolio includes more than 12 U.S and foreign patents and patent applications. Any patents within this portfolio that have issued or may yet issue would have a statutory expiration date in 2025.

In support of our program targeting miR-33, we have exclusively licensed from New York University, or NYU, patent rights encompassing the use of an anti-miR therapeutic targeting miR-33 for the treatment of atherosclerosis, metabolic syndrome and elevated triglycerides. In collaboration with us, Kathryn Moore, Ph.D. and colleagues at NYU demonstrated that inhibiting miR-33 has several therapeutic benefits, including reduction of atherosclerotic plaque size in an experimental model of atherosclerosis, in addition to reduction of serum triglycerides in non-human primates. The NYU-licensed patent rights include one U.S. application and one Patent Cooperation Treaty, or PCT, application. Any patents that may issue from these applications would have a statutory expiration date in 2031.

Our portfolio of exclusively and jointly owned patent and patent applications is currently composed of at least nine U.S. and foreign patents and more than 35 U.S. PCT and foreign applications. We are the sole owner of nine of the patents and over 30 of the pending applications. We jointly own at least five of the patents and pending applications including those claiming methods for treating liver cancer, including HCC, using anti-miRs targeting miR-21. The patents have statutory expiration dates in 2024, 2025, 2026, or 2029. Any patents that may issue from the pending applications would have statutory expiration dates between 2024 and 2032.

Table of Contents

Our founding companies, Alnylam and Isis, each own or otherwise have rights to numerous patents and patent applications concerning oligonucleotide technologies and a substantial number of these patents and applications have been exclusively licensed to us for use in the *micro*RNA field. The technologies covered in these patents and applications include various chemical modifications that are applicable to *micro*RNA therapeutics. Among the licensed patents or patent applications, those covering key chemical modifications for use in *micro*RNA drug products have statutory expiration dates in 2016, 2023 and 2027.

We have a co-exclusive license to the patent portfolio owned by Max-Planck-Gesellschaft, or MPG, which has been granted to us by Max-Planck-Innovation GmbH, or MI, a wholly-owned subsidiary of MPG acting as MPG s technology transfer agency. MPG and MI are collectively referred to herein as Max-Planck. This patent portfolio is based on the pioneering *micro*RNA research conducted by Thomas Tuschl, Ph.D. and colleagues at the Max-Planck Institute of Biophysical Chemistry, which led to the discovery of over 100 human *micro*RNA sequences, including *micro*RNAs that are the focus of several of our programs. The patent rights encompass the *micro*RNA gene sequences as well as the antisense sequences that are complementary to the *micro*RNAs and thus cover both *micro*RNA mimic and anti-miR products. Our license is co-exclusive with our founding companies, Alnylam and Isis, for the exploitation of the Max-Planck patent rights for therapeutic uses. In addition, we also have a co-exclusive license to develop and commercialize diagnostics based upon the Max-Planck patent rights contained in these applications. The Max-Planck licensed patent portfolio, referred to herein as the Tuschl 3 patents, includes at least 25 U.S. and foreign patents and patent applications. Any patents within this portfolio that have issued or may yet issue would have a statutory expiration date in 2022.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the date of filing the non-provisional application. In the United States, a patent s term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the U.S. Patent and Trademark Office in granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier-filed patent.

The term of a patent that covers an FDA-approved drug may also be eligible for patent term extension, which permits patent term restoration of a U.S. patent as compensation for the patent term lost during the FDA regulatory review process. The Hatch-Waxman Act permits a patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to the length of time the drug is under regulatory review. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug may be extended. Similar provisions are available in Europe and other foreign jurisdictions to extend the term of a patent that covers an approved drug. When possible, depending upon the length of clinical trials and other factors involved in the filing of a new drug application, or NDA, we expect to apply for patent term extensions for patents covering our *micro*RNA product candidates and their methods of use.

We may rely, in some circumstances, on trade secrets to protect our technology. However, trade secrets can be difficult to protect. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors and contractors. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our consultants, contractors or collaborators use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

Table of Contents

Our Technology Licenses

Max-Planck

Therapeutic license

Prior to 2011, our access to the Tuschl 3 patents was derived from agreements between Max-Planck and our founding companies, Alnylam and Isis, for exclusive use in *micro*RNA therapeutics. In April 2011, we entered into a direct, co-exclusive license with Max-Planck. The license provides to us, Alnylam and Isis, co-exclusively, access to the Tuschl 3 patents for therapeutic use. Max-Planck retains the right to practice the intellectual property licensed under the agreement for non-commercial purposes.

Under the terms of the license, we are permitted to sublicense our rights outright or as part of an alliance. The license requires that we use commercially reasonable diligence in developing and commercializing a product. In order to secure the license, we made an upfront payment of $400,000 to Max-Planck. We will be required to make payments based upon the initiation of clinical trials and/or product approval milestones totaling up to $1.6 million for each licensed product reaching such clinical stage. In addition to milestone payments, we will be required to pay royalties of a percentage of cumulative annual net sales of a licensed product commercialized by us or one of our strategic alliance partners. The percentage is in the low single digits, with the exact percentage depending upon whether the licensed product incorporates intellectual property covered by a Tuschl 3 patent that is still a pending application or, alternatively, an issued patent, and also upon the volume of annual sales. The royalties payable to Max-Planck are subject to reduction for any third party payments required to be made, with a minimum floor in the low single digits.

The longest lived patent rights licensed to us under the agreement are currently expected to expire in September 2022.

Diagnostic license

In addition, in June 2009, we entered into a co-exclusive license with Max-Planck for use of the Tuschl 3 patents for diagnostic purposes. Under the terms of the license, we made an aggregate initial payment to Max-Planck of 175,000 in three installments, with 75,000 paid in June 2009 and 50,000 paid in each of June 2010 and June 2011. In addition, we made annual maintenance payments of 10,000 in 2011 and 20,000 in 2012 and will make an increased annual maintenance payment commencing in 2013 and thereafter during the term of the agreement. In addition to maintenance payments, we will be required to pay royalties of a percentage of net sales of licensed products. The percentage is in the mid-single digits in the event we market the product and low end of the 10 to 20% range in the event we sell the product through a distributor. The royalties payable to Max-Planck are reduced by the royalties payable to third parties but only if aggregate royalties payable to Max-Planck and third parties exceed a percentage in the mid-10 to 20% range.

We are required to use commercially reasonable efforts to develop and commercialize products under the agreement. Under the terms of the agreement, Max-Planck is permitted to provide up to three additional co-exclusive licenses to its diagnostic patent rights. The longest lived patent rights licensed to us under the agreement are currently expected to expire in September 2022.

Max-Planck retains the right to practice the intellectual property licensed under the agreement for non-commercial purposes.

University of Würzburg

In May 2010, we exclusively licensed patent rights from the University of Würzburg which encompass the use of anti-miR therapeutics targeting miR-21 for the treatment of fibrosis, including kidney, liver, lung and cardiac fibrosis.

Table of Contents

The University of Würzburg has reserved the right to use the licensed intellectual property for academic and non-commercial purposes. We have the right to grant sublicenses to third parties under the agreement provided such sublicense is for the purpose of developing or commercializing a product. We must obtain the University of Würzburg s written consent to any such sublicense, which may not be unreasonably withheld. We must use commercially reasonable diligence in our efforts to develop, manufacture and commercialize a licensed product. We have assumed certain development milestone obligations and must report on our progress in achieving these milestones on an annual basis.

As a license issuance fee, we paid the University of Würzburg 300,000. In addition, upon commercialization of a product, we will pay to the University of Würzburg a percentage of net sales as a royalty. This royalty is in the low single digits and is reduced upon expiration of all patent claims covering the product. We also paid the University of Würzburg a partnership bonus of 200,000 upon entering into our strategic alliance agreement with Sanofi. Under the agreement, beginning January 1, 2020 and ending on the date we receive NDA approval for a licensed product, we will accrue a minimum royalty obligation of 150,000 per year, which will become payable upon approval of an NDA for a licensed product. After approval of an NDA for a licensed product, we will be required to pay the University of Würzburg an annual minimum royalty, which increases in the five years following approval up to a maximum of 3.0 million per year. The minimum royalties are creditable against actual royalties due and payable for the same calendar year.

In addition, we will be required to pay the University of Würzburg milestone payments of up to an aggregate of 1.75 million, based upon achievement of specified clinical and regulatory events. In the event we initiate a Phase 2 clinical trial for another indication with the same licensed product, we will be required to pay 50% of the milestone payments applicable to such milestone events. These milestone events are also tied to the due dates set forth in the commercialization plan but may be extended by delays caused by scientific challenges, regulatory requirements or other circumstances outside of our control. We must request an extension in writing explaining the cause for the delay and proposing new due dates. The University of Würzburg may accept the revised dates or reject them, in which case an arbitrator will set the revised dates.

The last to expire patent licensed to us under the agreement is currently expected to expire in February 2029.

Stanford University

In August 2005, Alnylam and Isis entered into a co-exclusive license agreement with Stanford, relating to its patent applications claiming the use of miR-122 to reduce the replication of HCV. Upon our formation, we received access to the Stanford technology as an affiliate of Alnylam and Isis. In July 2009, Isis assigned its rights and obligations under the license agreement to us.

Under the license agreement, we are permitted to research, develop, manufacture and commercialize therapeutics for the treatment and prevention of HCV and related conditions. Diagnostics and reagents are specifically excluded from the license. In addition, the license provides a non-exclusive right to research, develop, manufacture and commercialize therapeutics for all conditions or diseases other than HCV. Stanford retained the right, on behalf of itself and all other non-profit academic institutions, to practice the licensed patents for non-profit purposes.

We are permitted to sublicense our rights under the agreement in connection with a bona fide partnership seeking to research and/or develop products under a jointly prepared research plan and which also includes a license to our intellectual property or in association with providing services to a sublicensee. In the event we receive an upfront payment in connection with a sublicense, we are obligated to pay to Stanford a one-time fixed payment amount, which amount will vary depending upon the size of upfront payment we receive. We must also make an annual license maintenance payment during the term of the agreement. The maintenance payments are creditable against royalty payments made in the same year. We will be required to pay milestones for an

Table of Contents

exclusively licensed product which will be payable upon achievement of specified regulatory and clinical milestones in an aggregate amount of up to $400,000. Milestones for a non-exclusively licensed product will be payable upon achievement of the same milestones in an aggregate amount of up to $300,000 for the first such product and up to $200,000 for the second such product. Upon commercialization of a product, we will be required to pay to Stanford a percentage of net sales as a royalty. This percentage is in the low single digits. The payment will be reduced by other payments we are required to make to third parties until a minimum royalty has been reached.

The agreement requires that we use commercially reasonable efforts to develop, manufacture and commercialize a licensed product and we have agreed to meet certain development and commercialization milestones.

The last to expire patent licensed to us under the agreement is currently expected to expire in May 2025.

New York University

In March 2011, we entered into an exclusive license with NYU related to our miR-33 program. The license provides us the right to develop, manufacture and commercialize therapeutics for the treatment or prevention of atherosclerotic plaque and/or other metabolic disorders under NYU s patents. We are entitled to grant sublicenses under the agreement. NYU retains the right to practice the intellectual property licensed under the agreement for non-commercial purposes.

Under the terms of the agreement, we paid to NYU an upfront payment of $25,000. An equal additional payment will be required upon issuance of a patent containing a claim of treating or preventing disease. We will be required to make payments to NYU upon achievement of specified clinical and regulatory milestones of up to an aggregate of $925,000. These milestone payments will only be made after issuance of a therapeutic claim under the NYU patent applications. We are also required to pay royalties of a percentage of net sales for any product sold by us or a strategic alliance partner. The royalty rate is in the low single digits and is subject to reduction to a minimum amount in the event we are required to pay royalties to a third party. In the event we sublicense the NYU patents, NYU is also entitled to receive a percentage of the sublicense income received by us. The percentage payable depends upon the development stage of the program when the sublicense is completed with the highest percentage paid with submission of the first IND. The percentage thereafter declines until completion of the first Phase 2 clinical trial.

We are required, under the terms of the agreement, to use reasonable diligence to develop and commercialize a product and are required to provide NYU with annual reports detailing our progress in this regard. In particular, we are required to fulfill specific development and regulatory milestones by particular dates. The longest-lived patent rights covered by the agreement is currently expected to expire in August 2031.

Manufacturing

We contract with third parties to manufacture our compounds and intend to do so in the future. We do not own or operate and we do not expect to own or operate, facilities for product manufacturing, storage and distribution, or testing. We have personnel with extensive technical, manufacturing, analytical and quality experience and strong project management discipline to oversee contract manufacturing and testing activities, and to compile manufacturing and quality information for our regulatory submissions.

Manufacturing is subject to extensive regulations that impose various procedural and documentation requirements, which govern record keeping, manufacturing processes and controls, personnel, quality control and quality assurance, among others. Our systems and contractors are required to be in compliance with these regulations, and this is assessed regularly through monitoring of performance and a formal audit program.

Table of Contents

Drug substance

Our current drug substance supply chain involves various contractors that supply the raw materials and others that manufacture the anti-miR drug substance. We believe our current drug substance contractors have the scale, the systems and the experience to supply all planned IND-enabling studies, early clinical supplies and may be considered for later clinical trials and commercial manufacturing. To ensure continuity in our supply chain, we plan to establish supply arrangements with alternative suppliers for certain portions of our supply chain, as appropriate.

Our process uses common synthetic chemistry and readily available materials. We have established an ongoing program to identify possible process changes to improve purity, yield, manufacturability, and process changes will be implemented as warranted and appropriate. Based upon our knowledge of anti-sense compounds, we do not anticipate any stability issues with our anti-miR product candidates.

Drug product

Our drug product is expected to consist of the anti-miR drug substance in a powdered form formulated in a saline solution for injection. Drug product manufacturing uses common processes and readily available materials. When a potential product is ready to commence IND-enabling studies, we will be required to commence drug product stability studies.

Research and Development Expenses

In 2012, 2011 and 2010, research and development expenses were $20.3 million, $17.3 million and $20.2 million, respectively.

Competition

The biotechnology and pharmaceutical industries are characterized by intense and rapidly changing competition to develop new technologies and proprietary products. While we believe that our proprietary asset estate and scientific expertise in the *micro*RNA field provide us with competitive advantages, we face potential competition from many different sources, including larger and better-funded pharmaceutical companies. Not only must we compete with other companies that are focused on *micro*RNA therapeutics but any products that we may commercialize will have to compete with existing therapies and new therapies that may become available in the future.

We are aware of several companies that are working specifically to develop *micro*RNA therapeutics. These include the biotechnology companies Groove Biopharma, Inc., miRagen Therapeutics, Inc., Mirna Therapeutics, Inc., and Santaris Pharma A/S. These competitors also compete with us in recruiting human capital and securing licenses to complementary technologies or specific *micro*RNAs that may be critical to the success of our business. They also compete with us for potential funding from the pharmaceutical industry.

In addition, we expect that for each disease category for which we determine to develop and apply our *micro*RNA therapeutics there are other biotechnology companies that will compete against us by applying marketed products and development programs using technology other than *micro*RNA therapeutics. The key competitive factors that will affect the success of any of our development candidates, if commercialized, are likely to be their efficacy relative to such competing technologies, safety, convenience, price and the availability of reimbursement from government and other third-party payors. Our commercial opportunity could be reduced or eliminated if our competitors have products which are better in one or more of these categories.

Table of Contents

Our Leadership

Our executive team 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.

Garry E. Menzel, Ph.D., our Chief Operating Officer, is an accomplished strategy, finance and operations executive who previously served in global leadership roles as a Managing Director in the healthcare investment banking groups at The Goldman Sachs Group, Inc. and Credit Suisse AG and as a strategy consultant for Bain & Company, Inc.

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 board of directors are:

John M. Maraganore, Ph.D., Chairman of our board of directors since our conversion to a corporation in January 2009, and is the Chief Executive Officer and a director of Alnylam Pharmaceuticals.

David Baltimore, Ph.D., also serves on our scientific advisory board, and is a Professor of Biology at the California Institute of Technology. Dr. Baltimore also serves as a director of Amgen Inc., a publicly-held biotechnology company and several other private companies.

Bruce L.A. Carter, Ph.D. most recently served as Chief Executive Officer of ZymoGenetics, Inc., a publicly-held biotechnology company and also serves on the board of directors of Immune Design Corp., a privately-held biotechnology company and of Dr. Reddy s Laboratories Limited, a publicly-held pharmaceutical company.

Mark Foletta, CPA, most recently served as Senior Vice President, Finance and Chief Financial Officer of Amylin Pharmaceuticals, Inc. a publicly-held biotechnology company and also serves on the board of directors of AMN Healthcare Services, Inc.

Stelios Papadopoulos, Ph.D. serves as Chairman of the Board for Exelixis, Inc., a publicly-held biotechnology company, which he co-founded, and is a member of the board of directors of Biogen Idec Inc., a publicly-held biopharmaceutical company. Dr. Papadopoulos has also held various positions in the investment banking industry.

B. Lynne Parshall is the Chief Operating Officer and a director of Isis Pharmaceuticals and also serves as a director of Cytokinetics, Inc.

Doug Williams, Ph.D. is the Executive Vice President of Research and Development at Biogen Idec.

Kleanthis G. Xanthopoulos, Ph.D., is the President and Chief Executive Officer of Regulus Therapeutics and also serves on the board of directors of Apricus Biosciences, Inc., a publicly-held biotechnology company, Sente, Inc., Biotechnology Industry Association (BIO) and BIOCOM.

Table of Contents

Our executive team 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.

Government Regulation and Product Approval

Government authorities in the United States, at the federal, state and local level, and other countries extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, labeling, packaging, storage, record-keeping, promotion, advertising, distribution, post-approval monitoring and reporting, marketing and export and import of products such as those we are developing. Any product candidate that we develop must be approved by the FDA before it may be legally marketed in the United States and by the appropriate foreign regulatory agency before it may be legally marketed in foreign countries.

U.S. drug development process

In the United States, the FDA regulates drugs under the Federal Food, Drug and Cosmetic Act, or FDCA, and implementing regulations. Drugs are also subject to other federal, state and local statutes and regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant to administrative or judicial civil or criminal sanctions. FDA sanctions could include refusal to approve pending applications, withdrawal of an approval, clinical hold, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, debarment, restitution, disgorgement or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us. The process required by the FDA before a drug may be marketed in the United States generally involves the following:

completion of nonclinical laboratory tests, animal studies and formulation studies according to good laboratory practices, or GLP, or other applicable regulations;

submission to the FDA of an application for an IND, which must become effective before human clinical trials may begin;

performance of adequate and well-controlled human clinical trials according to the FDA s regulations commonly referred to as current good clinical practices, or GCPs, to establish the safety and efficacy of the proposed drug for its intended use;

submission to the FDA of an NDA for a new drug;

Table of Contents

satisfactory completion of an FDA inspection of the manufacturing facility or facilities where the drug is produced to assess compliance with the FDA s current good manufacturing practice standards, or cGMP, to assure that the facilities, methods and controls are adequate to preserve the drug s identity, strength, quality and purity;

potential FDA audit of the nonclinical and clinical trial sites that generated the data in support of the NDA; and

FDA review and approval of the NDA.

The lengthy process of seeking required approvals and the continuing need for compliance with applicable statutes and regulations require the expenditure of substantial resources and approvals are inherently uncertain.

Before testing any compounds with potential therapeutic value in humans, the drug candidate enters the preclinical testing stage. Preclinical tests, also referred to as nonclinical studies, include laboratory evaluations of product chemistry, toxicity and formulation, as well as animal studies to assess the potential safety and activity of the drug candidate. The conduct of the preclinical tests must comply with federal regulations and requirements including GLP. The sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA places the clinical trial on a clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. The FDA may also impose clinical holds on a drug candidate at any time before or during clinical trials due to safety concerns or non-compliance. Accordingly, we cannot be sure that submission of an IND will result in the FDA allowing clinical trials to begin, or that, once begun, issues will not arise that suspend or terminate such trial.

Clinical trials involve the administration of the drug candidate to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the trial sponsor s control. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria, and the parameters to be used to monitor subject safety. Each protocol must be submitted to the FDA as part of the IND. Clinical trials must be conducted in accordance with the FDA s regulations comprising the good clinical practices requirements. Further, each clinical trial must be reviewed and approved by an independent institutional review board, or IRB, at or servicing each institution at which the clinical trial will be conducted. An IRB is charged with protecting the welfare and rights of trial participants and considers such items as whether the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the form and content of the informed consent that must be signed by each clinical trial subject or his or her legal representative and must monitor the clinical trial until completed.

Human clinical trials are typically conducted in three sequential phases that may overlap or be combined:

Phase 1. The drug is initially introduced into healthy human subjects and tested for safety, dosage tolerance, absorption, metabolism, distribution and excretion. In the case of some products for severe or life-threatening diseases, especially when the product may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients.

Phase 2. The drug is evaluated in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance, optimal dosage and dosing schedule.

Phase 3. Clinical trials are undertaken to further evaluate dosage, clinical efficacy and safety in an expanded patient population at geographically dispersed clinical trial sites. These clinical trials are intended to establish the overall risk/benefit ratio of the product and provide an adequate basis for product labeling. Generally, two adequate and well-controlled Phase 3 clinical trials are required by the FDA for approval of an NDA.

Table of Contents

Post-approval clinical trials, sometimes referred to as Phase 4 clinical trials, may be conducted after initial marketing approval. These clinical trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication.

Annual progress reports detailing the results of the clinical trials must be submitted to the FDA and written IND safety reports must be promptly submitted to the FDA and the investigators for serious and unexpected adverse events or any finding from tests in laboratory animals that suggests a significant risk for human subjects. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, if at all. The FDA or the sponsor or its data safety monitoring board may suspend a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB s requirements or if the drug has been associated with unexpected serious harm to patients.

Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the drug as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug candidate and, among other things, must develop methods for testing the identity, strength, quality and purity of the final drug. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

U.S. review and approval processes

The results of product development, nonclinical studies and clinical trials, along with descriptions of the manufacturing process, analytical tests conducted on the chemistry of the drug, proposed labeling and other relevant information are submitted to the FDA as part of an NDA requesting approval to market the product. The submission of an NDA is subject to the payment of substantial user fees; a waiver of such fees may be obtained under certain limited circumstances.

In addition, under the Pediatric Research Equity Act, or PREA, an NDA or supplement to an NDA must contain data to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may grant deferrals for submission of data or full or partial waivers. Unless otherwise required by regulation, PREA does not apply to any drug for an indication for which orphan designation has been granted.

The FDA reviews all NDAs submitted to determine if they are substantially complete before it accepts them for filing. Once the submission is accepted for filing, the FDA begins an in-depth review of the NDA. Under the goals and policies agreed to by the FDA under the Prescription Drug User Fee Act, or PDUFA, the FDA has 10 months in which to complete its initial review of a standard NDA and respond to the applicant, and six months for a priority NDA. The FDA does not always meet its PDUFA goal dates for standard and priority NDAs. The review process and the PDUFA goal date may be extended by three months if the FDA requests or the NDA sponsor otherwise provides additional information or clarification regarding information already provided in the submission within the last three months before the PDUFA goal date.

After the NDA submission is accepted for filing, the FDA reviews the NDA to determine, among other things, whether the proposed product is safe and effective for its intended use, and whether the product is being manufactured in accordance with cGMP to assure and preserve the product s identity, strength, quality and purity. The FDA may refer applications for novel drug or biological products or drug or biological products which present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be

Table of Contents

approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. During the drug approval process, the FDA also will determine whether a risk evaluation and mitigation strategy, or REMS, is necessary to assure the safe use of the drug. If the FDA concludes a REMS is needed, the sponsor of the NDA must submit a proposed REMS; the FDA will not approve the NDA without a REMS, if required.

Before approving an NDA, the FDA will inspect the facilities at which the product is manufactured. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure that the clinical trials were conducted in compliance with IND study requirements. If the FDA determines that the application, manufacturing process or manufacturing facilities are not acceptable it will outline the deficiencies in the submission and often will request additional testing or information.

The NDA review and approval process is lengthy and difficult and the FDA may refuse to approve an NDA if the applicable regulatory criteria are not satisfied or may require additional clinical data or other data and information. Even if such data and information is submitted, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval. Data obtained from clinical trials are not always conclusive and the FDA may interpret data differently than we interpret the same data. The FDA will issue a complete response letter if the agency decides not to approve the NDA. The complete response letter usually describes all of the specific deficiencies in the NDA identified by the FDA. The deficiencies identified may be minor, for example, requiring labeling changes, or major, for example, requiring additional clinical trials. Additionally, the complete response letter may include recommended actions that the applicant might take to place the application in a condition for approval. If a complete response letter is issued, the applicant may either resubmit the NDA, addressing all of the deficiencies identified in the letter, or withdraw the application.

If a product receives regulatory approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling. In addition, the FDA may require post marketing clinical trials, sometimes referred to as Phase 4 clinical trials testing, which involves clinical trials designed to further assess a drug safety and effectiveness and may require testing and surveillance programs to monitor the safety of approved products that have been commercialized.

Orphan drug designation

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biological product intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making a drug or biological product available in the United States for this type of disease or condition will be recovered from sales of the product. Orphan product designation must be requested before submitting an NDA. After the FDA grants orphan product designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If a product that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications to market the same drug or biological product for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity. Competitors, however, may receive approval of different products for the indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for

Table of Contents

which the orphan product has exclusivity. Orphan product exclusivity also could block the approval of one of our products for seven years if a competitor obtains approval of the same drug or biological product as defined by the FDA or if our drug candidate is determined to be contained within the competitor s product for the same indication or disease. If a drug or biological product designated as an orphan product receives marketing approval for an indication broader than what is designated, it may not be entitled to orphan product exclusivity. Orphan drug status in the European Union has similar but not identical benefits in the European Union.

Expedited development and review programs

The FDA has a Fast Track program that is intended to expedite or facilitate the process for reviewing new drugs and biological products that meet certain criteria. Specifically, new drugs and biological products are eligible for Fast Track designation if they are intended to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. Unique to a Fast Track product, the FDA may consider for review sections of the NDA on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the NDA, the FDA agrees to accept sections of the NDA and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the NDA.

Any product submitted to the FDA for marketing, including a Fast Track program, may also be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval. Any product is eligible for priority review if it has the potential to provide safe and effective therapy where no satisfactory alternative therapy exists or a significant improvement in the treatment, diagnosis or prevention of a disease compared to marketed products. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug or biological product designated for priority review in an effort to facilitate the review. Additionally, a product may be eligible for accelerated approval. Drug or biological products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval, which means that they may be approved on the basis of adequate and well-controlled clinical trials establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. As a condition of approval, the FDA may require that a sponsor of a drug or biological product receiving accelerated approval perform adequate and well-controlled post-marketing clinical trials. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product. Fast Track designation, priority review and accelerated approval do not change the standards for approval but may expedite the development or approval process.

Post-approval requirements

Any drug products for which we or our strategic alliance partners receive FDA approvals are subject to continuing regulation by the FDA, including, among other things, record-keeping requirements, reporting of adverse experiences with the product, providing the FDA with updated safety and efficacy information, product sampling and distribution requirements, complying with certain electronic records and signature requirements and complying with FDA promotion and advertising requirements, which include, among others, standards for direct-to-consumer advertising, promoting drugs for uses or in patient populations that are not described in the drug s approved labeling (known as off-label use), industry-sponsored scientific and educational activities, and promotional activities involving the internet. Failure to comply with FDA requirements can have negative consequences, including adverse publicity, enforcement letters from the FDA, mandated corrective advertising or communications with doctors, and civil or criminal penalties. Although physicians may prescribe legally available drugs for off-label uses, manufacturers may not market or promote such off-label uses.

We will rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of any products that we may commercialize. Our strategic alliance partners may also utilize third

Table of Contents

parties for some or all of a product we are developing with such strategic alliance partner. Manufacturers of our products are required to comply with applicable FDA manufacturing requirements contained in the FDA s cGMP regulations. cGMP regulations require among other things, quality control and quality assurance as well as the corresponding maintenance of records and documentation. Drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP and other laws. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance. Discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved NDA, including withdrawal of the product from the market. In addition, changes to the manufacturing process generally require prior FDA approval before being implemented and other types of changes to the approved product, such as adding new indications and additional labeling claims, are also subject to further FDA review and approval.

The FDA also may require post-marketing testing, known as Phase 4 testing, risk minimization action plans and surveillance to monitor the effects of an approved product or place conditions on an approval that could restrict the distribution or use of the product.

U.S. patent term restoration and marketing exclusivity

Depending upon the timing, duration and specifics of the FDA approval of the use of our drug candidates, some of our United States patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product s approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of an NDA plus the time between the submission date of an NDA and the approval of that application. Only one patent applicable to an approved drug is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. The United States Patent and Trademark Office, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we may intend to apply for restoration of patent term for one of our currently owned or licensed patents to add patent life beyond its current expiration date, depending on the expected length of the clinical trials and other factors involved in the filing of the relevant NDA.

Market exclusivity provisions under the FDCA can also delay the submission or the approval of certain applications of other companies seeking to reference another company s NDA. The FDCA provides a five-year period of non-patent marketing exclusivity within the United States to the first applicant to obtain approval of an NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the action of the drug substance. During the exclusivity period, the FDA may not accept for review an abbreviated new drug application, or ANDA, or a 505(b)(2) NDA submitted by another company for another version of such drug where the applicant does not own or have a legal right of reference to all the data required for approval. However, an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement to one of the patents listed with the FDA by the innovator NDA holder. The FDCA also provides three years of marketing exclusivity for an NDA, or supplement to an existing NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, for example new indications, dosages or strengths of an existing drug. This three-year exclusivity covers only the conditions associated with the new clinical investigations and does not prohibit the FDA from approving ANDAs for drugs containing the original active agent. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA. However, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the

Table of Contents

preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness. Pediatric exclusivity is another type of regulatory market exclusivity in the United States. Pediatric exclusivity, if granted, adds six months to existing exclusivity periods and patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of a pediatric trial in accordance with an FDA-issued Written Request for such a trial.

U.S. Foreign Corrupt Practices Act

The U.S. Foreign Corrupt Practices Act, or FCPA, prohibits certain individuals and entities, including us, from promising, paying, offering to pay, or authorizing the payment of anything of value to any foreign government official, directly or indirectly, to obtain or retain business or an improper advantage. The U.S. Department of Justice and the U.S. Securities and Exchange Commission, or SEC, have increased their enforcement efforts with respect to the FCPA. Violations of the FCPA may result in large civil and criminal penalties and could result in an adverse effect on a company s reputation, operations, and financial condition. A company may also face collateral consequences such as debarment and the loss of export privileges.

Federal and state fraud and abuse laws

In addition to FDA restrictions on marketing of pharmaceutical products, several other types of state and federal laws have been applied to restrict certain business practices in the biopharmaceutical industry in recent years. These laws include anti-kickback statutes and false claims statutes.

The federal Anti-Kickback Statute prohibits, among other things, knowingly and willfully offering, paying, soliciting, or receiving remuneration to induce or in return for purchasing, leasing, ordering, or arranging for the purchase, lease, or order of any healthcare item or service reimbursable under Medicare, Medicaid, or other federally financed healthcare programs. The term remuneration has been broadly interpreted to include anything of value, including for example, gifts, discounts, the furnishing of supplies or equipment, credit arrangements, payments of cash, waivers of payment, ownership interests and providing anything at less than its fair market value. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, and formulary managers on the other. Although there are a number of statutory exemptions and regulatory safe harbors protecting certain common activities from prosecution, the exemptions and safe harbors are drawn narrowly, and our practices may not in all cases meet all of the criteria for statutory exemptions or safe harbor protection. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases, or recommendations may be subject to scrutiny if they do not qualify for an exemption or safe harbor. . Several courts have interpreted the statute s intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the statute has been violated. The reach of the Anti-Kickback Statute was also broadened by the Patient Protection and Affordable Health Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively the PPACA, which, among other things, amends the intent requirement of the federal Anti-Kickback Statute. Pursuant to the statutory amendment, a person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, the PPACA provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act (discussed below) or the civil monetary penalties statute, which imposes penalties against any person who is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent.

The federal False Claims Act prohibits any person from knowingly presenting, or causing to be presented, a false claim for payment to the federal government. Recently, several pharmaceutical and other healthcare companies have been prosecuted under these laws for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have been

Table of Contents

prosecuted for causing false claims to be submitted because of the companies marketing of the product for unapproved, and thus non-reimbursable, uses. Many states also have statutes or regulations similar to the federal Anti-Kickback Statute and False Claims Act, which state laws apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payer. Also, the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created new federal criminal statutes that prohibit knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private third-party payers and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services.

Because of the breadth of these laws and the narrowness of the federal Anti-Kickback Statute s safe harbors, it is possible that some of our business activities could be subject to challenge under one or more of such laws. Such a challenge could have a material adverse effect on our business, financial condition and results of operations. If we obtain FDA approval for any of our product candidates and begin commercializing those products in the United States, our operations may be directly, or indirectly through our customers, distributors, or other business partners, subject to various federal and state fraud and abuse laws, including, without limitation, anti-kickback statutes and false claims statutes. These laws may impact, among other things, our proposed sales, marketing and education programs.

In addition, we may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology and Clinical Health Act, or HITECH, and its implementing regulations, imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA s privacy and security standards directly applicable to business associates independent contractors or agents of covered entities that receive or obtain protected health information in connection with providing a service on behalf of a covered entity. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney s fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

If our operations are found to be in violation of any of the federal and state laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including criminal and significant civil monetary penalties, damages, fines, imprisonment, exclusion of products from reimbursement under government programs, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. To the extent that any of our product candidates are ultimately sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws, and implementation of corporate compliance programs and reporting of payments or transfers of value to healthcare professionals.

In the United States and foreign jurisdictions, there have been a number of legislative and regulatory changes to the healthcare system that could affect our future results of operations. In particular, there have been and continue to be a number of initiatives at the United States federal and state levels that seek to reduce healthcare costs. The Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, imposed new requirements for the distribution and pricing of prescription drugs for Medicare beneficiaries. Under Part D, Medicare beneficiaries may enroll in prescription drug plans offered by private entities which will provide coverage of outpatient prescription drugs. Part D plans include both stand-alone prescription drug benefit plans and prescription drug coverage as a supplement to Medicare Advantage plans. Unlike Medicare Part A and B, Part D coverage is not standardized. Part D prescription drug plan sponsors are not required to pay for all covered Part D drugs, and each drug plan can develop its own drug formulary that identifies which drugs it will cover and at what

Table of Contents

tier or level. However, Part D prescription drug formularies must include drugs within each therapeutic category and class of covered Part D drugs, though not necessarily all the drugs in each category or class. Any formulary used by a Part D prescription drug plan must be developed and reviewed by a pharmacy and therapeutic committee. Government payment for some of the costs of prescription drugs may increase demand for our products for which we receive marketing approval. However, any negotiated prices for our products covered by a Part D prescription drug plan will likely be lower than the prices we might otherwise obtain. Moreover, while the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in payment that results from Medicare Part D may result in a similar reduction in payments from non-governmental payors.

The American Recovery and Reinvestment Act of 2009 provides funding for the federal government to compare the effectiveness of different treatments for the same illness. A plan for the research will be developed by the Department of Health and Human Services, the Agency for Healthcare Research and Quality and the National Institutes for Health, and periodic reports on the status of the research and related expenditures will be made to Congress. Although the results of the comparative effectiveness studies are not intended to mandate coverage policies for public or private payors, it is not clear what effect, if any, the research will have on the sales of any product, if any such product or the condition that it is intended to treat is the subject of a study. It is also possible that comparative effectiveness research demonstrating benefits in a competitor s product could adversely affect the sales of our product candidates. If third-party payors do not consider our products to be cost-effective compared to other available therapies, they may not cover our products as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our products on a profitable basis.

Most recently, in March 2010 the PPACA was enacted, which includes measures to significantly change the way healthcare is financed by both governmental and private insurers. Among the provisions of the PPACA of greatest importance to the pharmaceutical and biotechnology industry are the following:

- an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs, that began in 2011;

- an increase in the rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13% of the average manufacturer price for branded and generic drugs, respectively;

- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts to negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer s outpatient drugs to be covered under Medicare Part D;

- extension of manufacturers Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;

- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for certain individuals with income at or below 133% of the Federal Poverty Level beginning in 2014, thereby potentially increasing manufacturers Medicaid rebate liability;

- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;

- new requirements to report certain financial arrangements with physicians and teaching hospitals, as defined in the PPACA and its implementing regulations, including reporting any transfer of value made or distributed to teaching hospitals, prescribers and other healthcare providers and reporting any ownership and investment interests held by physicians and their immediate family members and applicable group purchasing organizations during the preceding calendar year, with data collection to be required beginning August 1, 2013 and reporting to the Centers for Medicare & Medicaid Services, or CMS, to be required by March 31, 2014 and by the 90th day of each subsequent calendar year;

22

Table of Contents

a new requirement to annually report drug samples that manufacturers and distributors provide to physicians, effective April 1, 2012;

expansion of health care fraud and abuse laws, including the False Claims Act and the Anti-Kickback Statute, new government investigative powers, and enhanced penalties for noncompliance;

a licensure framework for follow-on biologic products;

a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;

creation of the Independent Payment Advisory Board which, beginning in 2014, will have authority to recommend certain changes to the Medicare program that could result in reduced payments for prescription drugs and those recommendations could have the effect of law even if Congress does not act on the recommendations; and

establishment of a Center for Medicare Innovation at CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending that began on January 1, 2011.

Many of the details regarding the implementation of the PPACA are yet to be determined, and at this time, it remains unclear the full effect that the PPACA would have on our business. On June 28, 2012, the US Supreme Court upheld the constitutionality of the PPACA, excepting certain provisions that would have required each state to expand its Medicaid programs or risk losing all of the state s Medicaid funding. At this time, it remains unclear whether there will be any further changes made to the PPACA, whether in part or in its entirety. Some states have indicated that they intend to not implement certain sections of the PPACA, and some members of the US Congress are still working to repeal the PPACA. We cannot predict whether these challenges will continue or other proposals will be made or adopted, or what impact these efforts may have on us.

Europe / rest of world government regulation

In addition to regulations in the United States, we and our strategic alliance partners will be subject to a variety of regulations in other jurisdictions governing, among other things, clinical trials and any commercial sales and distribution of our products.

Whether or not we or our collaborators obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application much like the IND prior to the commencement of human clinical trials. In the European Union, for example, a clinical trial application, or CTA, must be submitted to each country s national health authority and an independent ethics committee, much like the FDA and IRB, respectively. Once the CTA is approved in accordance with a country s requirements, clinical trial development may proceed.

The requirements and process governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, the clinical trials are conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

To obtain regulatory approval of an investigational drug or biological product under European Union regulatory systems, we or our strategic alliance partners must submit a marketing authorization application. The application used to file the NDA or BLA in the United States is similar to that required in the European Union, with the exception of, among other things, country-specific document requirements.

For other countries outside of the European Union, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary

Table of Contents

from country to country. In all cases, again, the clinical trials are conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

If we or our strategic alliance partners fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Employees

As of December 31, 2012, we had 72 employees, of which 66 were full-time employees. Of these full-time employees, 52 employees are engaged in research and development activities and 14 employees are engaged in finance, legal, human resources, facilities and general management. We have no collective bargaining agreements with our employees and we have not experienced any work stoppages. We consider our relations with our employees to be good.

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. Our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, and amendments to reports filed pursuant to Sections 13(a) and 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, are available free of charge on our website as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. The SEC maintains an internet site that contains our public filings with the SEC and other information regarding the Company, at www.sec.gov. These reports and other information concerning the Company may also be accessed at the SEC s Public Reference Room at 100 F Street, NE, Washington, DC 20549. The public may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. The contents of these websites are not incorporated into this Annual Report. Further, our references to the URLs for these websites are intended to be 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 Annual Report contains references to our trademarks and to trademarks belonging to other entities. Solely for convenience, trademarks and trade names referred to in this Annual Report, including logos, artwork and other visual displays, may appear without the ® or symbols, but such references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights or the rights of the applicable licensor to these trademarks and trade names. We do not intend our use or display of other companies trade names or trademarks to imply a relationship with, or endorsement or sponsorship of us by, any other companies.

We are an emerging growth company, as defined in the Jumpstart Our Business Startups Act of 2012. We will remain an emerging growth company until the earlier of (1) the last day of the fiscal year (a) following the fifth anniversary of our initial public offering in October 2012, (b) in which we have total annual gross revenue of at least $1.0 billion, or (c) in which we are deemed to be a large accelerated filer, and (2) the date on which we have issued more than $1.0 billion in non-convertible debt during the prior three-year period. We refer to the Jumpstart Our Business Startups Act of 2012 herein as the JOBS Act, and references herein to emerging growth company shall have the meaning associated with it in the JOBS Act.

Table of Contents

Item 1A. Risk Factors.

Except for the historical information contained herein or incorporated by reference, this Annual Report and the information incorporated by reference contains forward-looking statements that involve risks and uncertainties. These statements include projections about our accounting and finances, plans and objectives for the future, future operating and economic performance and other statements regarding future performance. These statements are not guarantees of future performance or events. Our actual results may differ materially from those discussed here. Factors that could cause or contribute to differences in our actual results include those discussed in the following section, as well as those discussed in Part II, Item 7 entitled Management s Discussion and Analysis of Financial Condition and Results of Operations and elsewhere throughout this Annual Report and in any other documents incorporated by reference into this Annual Report. You should consider carefully the following risk factors, together with all of the other information included or incorporated in this Annual Report. Each of these risk factors, either alone or taken together, could adversely affect our business, operating results and financial condition, as well as adversely affect the value of an investment in our common stock. There may be additional risks that we do not presently know of or that we currently believe are immaterial which could also impair our business and financial position.

RISKS RELATED TO OUR FINANCIAL CONDITION AND NEED FOR ADDITIONAL CAPITAL

We have a limited operating history, have incurred significant losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future.

We are a preclinical-stage, biopharmaceutical discovery and development company, formed in 2007, with a limited operating history. Since inception, our operations have been primarily limited to organizing and staffing our company, acquiring and in-licensing intellectual property rights, developing our *micro*RNA product platform, undertaking basic research around *micro*RNA targets and conducting preclinical studies for our initial programs. We have not yet identified product candidates for clinical development, initiated a clinical trial or obtained regulatory approval for any product candidates. Consequently, any predictions about our future success or viability, or any evaluation of our business and prospects, may not be accurate.

We have incurred losses in each year since our inception in September 2007. Our net losses were $17.4 million, $7.6 million and $15.6 million for the years ended December 31, 2012, 2011 and 2010, respectively. As of December 31, 2012, we had an accumulated deficit of $60.4 million.

We have devoted most of our financial resources to research and development, including our preclinical development activities. To date, we have financed our operations primarily through the sale of equity securities and convertible debt and from revenue received from our strategic alliance partners. We have entered into strategic alliances with Sanofi to develop our miR-21 programs for hepatocellular carcinoma, or HCC, and kidney fibrosis, with GSK, to develop our miR-122 program for hepatitis C virus infection, or HCV, and with AstraZeneca, to develop our miR-33 program for atherosclerosis. Under our agreement with GSK, GSK has an option to obtain exclusive worldwide licenses for the development, manufacture and commercialization of potential product candidates selected from our *micro*RNA product platform. If GSK exercises its option to obtain a license to develop, manufacture and commercialize such product candidates, GSK will assume responsibility for funding and conducting further clinical development and commercialization activities for such product candidates. However, if GSK does not exercise its option within the timeframes that we expect, or at all, or if Sanofi terminates its agreement with us, we will be responsible for funding further development of these product candidates and may not have the resources to do so unless we are able to enter into another strategic alliance for these product candidates. The size of our future net losses will depend, in part, on the rate of future expenditures and our ability to obtain funding through equity or debt financings, strategic alliances or grants. We have not initiated clinical development of any product candidate to date and it will be several years, if ever, before we have a product candidate ready for commercialization. Even if we or our strategic alliance partners successfully

Table of Contents

obtain regulatory approval to market a product candidate, our revenues will also depend upon the size of any markets in which our product candidates have received market approval, and our ability to achieve sufficient market acceptance and adequate market share for our products.

We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. The net losses we incur may fluctuate significantly from quarter to quarter. We anticipate that our expenses will increase substantially if and as we: continue our research and preclinical development of our future product candidates, both independently and under our strategic alliance agreements; seek to identify additional *micro*RNA targets and product candidates; acquire or in-license other products and technologies; initiate clinical trials for our product candidates; seek marketing approvals for our product candidates that successfully complete clinical trials; ultimately establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain marketing approval; maintain, expand and protect our intellectual property portfolio; hire additional clinical, quality control and scientific personnel; and create additional infrastructure to support our operations as a public company and our product development and planned future commercialization efforts.

We have never generated any revenue from product sales and may never be profitable.

Our ability to generate revenue and achieve profitability depends on our ability, alone or with strategic alliance partners, to successfully complete the development of, obtain the necessary regulatory approvals for and commercialize product candidates. We do not anticipate generating revenues from sales of products for the foreseeable future, if ever. Our ability to generate future revenues from product sales depends heavily on our success in:

- identifying and validating new *micro*RNAs as therapeutic targets;
- completing our research and preclinical development of future product candidates;
- initiating and completing clinical trials for future product candidates;
- seeking and obtaining marketing approvals for future product candidates that successfully complete clinical trials;
- establishing and maintaining supply and manufacturing relationships with third parties;
- launching and commercializing future product candidates for which we obtain marketing approval, with an alliance partner or, if launched independently, successfully establishing a sales force, marketing and distribution infrastructure;
- maintaining, protecting and expanding our intellectual property portfolio; and
- attracting, hiring and retaining qualified personnel.

Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to predict the timing or amount of increased expenses and when we will be able to achieve or maintain profitability, if ever. In addition, our expenses could increase beyond expectations if we are required by the FDA or foreign regulatory agencies to perform studies and trials in addition to those that we currently anticipate.

Even if one or more of the future product candidates that we independently develop is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product candidate. Even if we are able to generate revenues from the sale of any

approved products, we may not become profitable and may need to obtain additional funding to continue operations.

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

Table of Contents

ongoing activities, particularly as we advance our product candidates toward clinical programs. We will need to seek alternative financing or change our operational plans to continue as a going concern. 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 expect that our existing cash and cash equivalents, together with interest, will be sufficient to fund our current operations into 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 nonclinical studies, required to file an investigational new drug application, or IND, which may occur as early as 2014, we may have adverse results requiring that we find new product candidates, or 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:

- significantly delay, scale back or discontinue the development or commercialization of any future product candidates;
- 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
- 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 may sell our equity or debt securities to fund our operations, which may result in dilution to our stockholders and impose restrictions on our business.

In order to raise additional funds to support our operations, we may sell our equity or debt securities, which would result in dilution to all of our stockholders or impose restrictive covenants that adversely impact our business. The sale of additional equity or convertible securities would result in the issuance of additional shares of our capital stock and dilution to all of our stockholders. The incurrence of indebtedness would result in increased fixed payment obligations and could also result in certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. If we are unable to expand our operations or otherwise capitalize on our business opportunities, our business, financial condition and results of operations could be materially adversely affected and we may not be able to meet our debt service obligations.

Table of Contents

RISKS RELATED TO THE DISCOVERY AND DEVELOPMENT OF PRODUCT CANDIDATES

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

We have concentrated our therapeutic product research and development efforts on *micro*RNA technology, and our future success depends on the successful development of this technology and products based on our *micro*RNA product platform. Neither we nor any other company has received regulatory approval to market therapeutics targeting *micro*RNAs. The scientific discoveries that form the basis for our efforts to discover and develop product candidates are relatively new. The scientific evidence to support the feasibility of developing product candidates based on these discoveries is both preliminary and limited. If we do not successfully develop and commercialize product candidates based upon our technological approach, we may not become profitable and the value of our common stock may decline.

Further, our focus solely on *micro*RNA technology for developing drugs as opposed to multiple, more proven technologies for drug development increases the risks associated with the ownership of our common stock. If we are not successful in developing any product candidates using *micro*RNA technology, we may be required to change the scope and direction of our product development activities. In that case, we may not be able to identify and implement successfully an alternative product development strategy.

We may not be successful in our efforts to identify or discover potential product candidates.

The success of our business depends primarily upon our ability to identify, develop and commercialize *micro*RNA therapeutics. Our research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development for a number of reasons, including:

- our research methodology or that of our strategic alliance partners may be unsuccessful in identifying potential product candidates;
- potential product candidates may be shown to have harmful side effects or may have other characteristics that may make the products unmarketable or unlikely to receive marketing approval; or
- our strategic alliance partners may change their development profiles for potential product candidates or abandon a therapeutic area.

If any of these events occur, we may be forced to abandon our development efforts for a program or programs, which would have a material adverse effect on our business and could potentially cause us to cease operations. Research programs to identify new product candidates require substantial technical, financial and human resources. We may focus our efforts and resources on potential programs or product candidates that ultimately prove to be unsuccessful.

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 have invested a significant portion of our efforts and financial resources in the identification and preclinical development of product candidates that target *micro*RNAs. Our ability to generate product revenues, which we do not expect will occur for many years, if ever, will depend heavily on the successful development and eventual commercialization of our future product candidates.

The success of our future product candidates will depend on several factors, including the following:

- successful completion of preclinical studies and clinical trials;

receipt of marketing approvals from applicable regulatory authorities;

Table of Contents

- obtaining and maintaining patent and trade secret protection for future product candidates;
- establishing and maintaining manufacturing relationships with third parties or establishing our own manufacturing capability; and
- successfully commercializing our products, if and when approved, whether alone or in collaboration with others.

If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully complete the development of, or commercialize, our product candidates, which would materially harm our business.

If clinical trials of our future product candidates fail to demonstrate safety and efficacy to the satisfaction of regulatory authorities or do not otherwise produce positive results, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our future product candidates.

Before obtaining marketing approval from regulatory authorities for the sale of future product candidates, we or our strategic alliance partners must then conduct extensive clinical trials to demonstrate the safety and efficacy of the product candidates in humans. Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. A failure of one or more clinical trials can occur at any stage of testing. The outcome of preclinical studies and early clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial do not necessarily predict final results. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval for their products.

Events which may result in a delay or unsuccessful completion of clinical development include:

- delays in reaching an agreement with the FDA on final trial design;
- imposition of a clinical hold following an inspection of our clinical trial operations or trial sites by the FDA or other regulatory authorities;
- delays in reaching agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical trial sites;
- our inability to adhere to clinical trial requirements directly or with third parties such as CROs;
- delays in obtaining required institutional review board approval at each clinical trial site;
- delays in recruiting suitable patients to participate in a trial;
- delays in the testing, validation, manufacturing and delivery of the product candidates to the clinical sites;
- delays in having patients complete participation in a trial or return for post-treatment follow-up;

delays caused by patients dropping out of a trial due to product side effects or disease progression;

clinical sites dropping out of a trial to the detriment of enrollment;

time required to add new clinical sites; or

delays by our contract manufacturers to produce and deliver sufficient supply of clinical trial materials.

If we or our strategic alliance partners are required to conduct additional clinical trials or other testing of any future product candidates beyond those that are currently contemplated, are unable to successfully complete

Table of Contents

clinical trials of any such product candidates or other testing, or if the results of these trials or tests are not positive or are only modestly positive or if there are safety concerns, we or our strategic alliance partners may:

- be delayed in obtaining marketing approval for our future product candidates;
- not obtain marketing approval at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings;
- be subject to additional post-marketing testing requirements; or
- have the product removed from the market after obtaining marketing approval.

Our product development costs will also increase if we experience delays in testing or marketing approvals. We do not know whether any clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Significant clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do, which would impair our ability to successfully commercialize our product candidates and may harm our business and results of operations. Any inability to successfully complete preclinical and clinical development, whether independently or with our strategic alliance partners, could result in additional costs to us or impair our ability to generate revenues from product sales, regulatory and commercialization milestones and royalties.

Any of our future product candidates may cause adverse effects or have other properties that could delay or prevent their regulatory approval or limit the scope of any approved label or market acceptance.

Adverse events, or AEs, caused by our future product candidates could cause us, other reviewing entities, clinical trial sites or regulatory authorities to interrupt, delay or halt clinical trials and could result in the denial of regulatory approval. Certain oligonucleotide therapeutics have shown injection site reactions and pro-inflammatory effects and may also lead to impairment of kidney or liver function. There is a risk that our future product candidates may induce similar adverse events.

If AEs are observed in any clinical trials of our future product candidates, including those that our strategic partners may develop under our alliance agreements, our or our partners ability to obtain regulatory approval for product candidates may be negatively impacted.

Further, if any of our future products, if and when approved for commercial sale, cause serious or unexpected side effects, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw their approval of the product or impose restrictions on its distribution in the form of a modified risk evaluation and mitigation strategy;
- regulatory authorities may require the addition of labeling statements, such as warnings or contraindications;
- we may be required to change the way the product is administered or conduct additional clinical trials;

we could be sued and held liable for harm caused to patients; or

our reputation may suffer.

Any of these events could prevent us or our partners from achieving or maintaining market acceptance of the affected product and could substantially increase the costs of commercializing our future products and impair our ability to generate revenues from the commercialization of these products either by us or by our strategic alliance partners.

Table of Contents

Even if we complete the necessary preclinical studies and clinical trials, we cannot predict whether or when we will obtain regulatory approval to commercialize a product candidate and we cannot, therefore, predict the timing of any revenue from a future product.

Neither we nor our strategic alliance partners can commercialize a product until the appropriate regulatory authorities, such as the FDA, have reviewed and approved the product candidate. The regulatory agencies may not complete their review processes in a timely manner, or we may not be able to obtain regulatory approval. Additional delays may result if an FDA Advisory Committee recommends restrictions on approval or recommends non-approval. In addition, we or our strategic alliance partners may experience delays or rejections based upon additional government regulation from future legislation or administrative action, or changes in regulatory agency policy during the period of product development, clinical trials and the review process.

Even if we obtain regulatory approval for a product candidate, we will still face extensive regulatory requirements and our products may face future development and regulatory difficulties.

Even if we obtain regulatory approval in the United States, the FDA may still impose significant restrictions on the indicated uses or marketing of our future product candidates, or impose ongoing requirements for potentially costly post-approval studies or post-market surveillance. The holder of an approved new drug application, or NDA, is obligated to monitor and report AEs and any failure of a product to meet the specifications in the NDA. The holder of an approved NDA must also submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process. Advertising and promotional materials must comply with FDA rules and are subject to FDA review, in addition to other potentially applicable federal and state laws.

In addition, drug product manufacturers and their facilities are subject to payment of user fees and continual review and periodic inspections by the FDA and other regulatory authorities for compliance with current good manufacturing practices, or cGMP, and adherence to commitments made in the NDA. If we or a regulatory agency discovers previously unknown problems with a product such as AEs of unanticipated severity or frequency, or problems with the facility where the product is manufactured, a regulatory agency may impose restrictions relative to that product or the manufacturing facility, including requiring recall or withdrawal of the product from the market or suspension of manufacturing.

If we or our partners fail to comply with applicable regulatory requirements following approval of any of our future product candidates, a regulatory agency may:

- issue a warning letter asserting that we are in violation of the law;
- seek an injunction or impose civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical trials;
- refuse to approve a pending NDA or supplements to an NDA submitted by us;
- seize product; or
- refuse to allow us to enter into supply contracts, including government contracts.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize our future products and generate revenues.

We may not be successful in obtaining or maintaining necessary rights to *micro*RNA targets, drug compounds and processes for our development pipeline through acquisitions and in-licenses.

Presently we have rights to the intellectual property, through licenses from third parties and under patents that we own, to modulate only a subset of the known *micro*RNA targets. Because our programs may involve a

Table of Contents

range of *micro*RNA targets, including targets that require the use of proprietary rights held by third parties, the growth of our business will likely depend in part on our ability to acquire, in-license or use these proprietary rights. In addition, our future product candidates may require specific formulations to work effectively and efficiently and these rights may be held by others. We may be unable to acquire or in-license any compositions, methods of use, processes or other third-party intellectual property rights from third parties that we identify. The licensing and acquisition of third-party intellectual property rights is a competitive area, and a number of more established companies are also pursuing strategies to license or acquire third-party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size, cash resources and greater clinical development and commercialization capabilities.

For example, we sometimes collaborate with U.S. and foreign academic institutions to accelerate our preclinical research or development under written agreements with these institutions. Typically, these institutions provide us with an option to negotiate a license to any of the institution s rights in technology resulting from the collaboration. Regardless of such right of first negotiation for intellectual property, we may be unable to negotiate a license within the specified time frame or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to other parties, potentially blocking our ability to pursue our program.

In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment. If we are unable to successfully obtain rights to required third-party intellectual property rights, our business, financial condition and prospects for growth could suffer.

We may use our financial and human resources to pursue a particular research program or product candidate and fail to capitalize on programs or product candidates that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial and human resources, we intend to leverage our existing strategic alliance agreements and enter into new strategic alliance agreements for the development and commercialization of our programs and potential product candidates in indications with potentially large commercial markets such as HCC, fibrosis and HCV, while focusing our internal development resources and any internal sales and marketing organization that we may establish on research programs and future product candidates for selected markets, such as orphan diseases. As a result, we may forego or delay pursuit of opportunities with other programs or product candidates or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and future product candidates for specific indications may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through strategic alliance, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate, or we may allocate internal resources to a product candidate in a therapeutic area in which it would have been more advantageous to enter into a partnering arrangement.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we

Table of Contents

could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties.

Although we maintain workers compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials or other work-related injuries, this insurance may not provide adequate coverage against potential liabilities. In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

RISKS RELATED TO OUR RELIANCE ON THIRD PARTIES

We will depend upon 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 and we may be unable to generate revenues from our development programs.

We are likely to depend upon third party alliance partners for financial and scientific resources for the clinical development and commercialization of certain of our *micro*RNA product candidates. These strategic alliances will likely provide us with limited control over the course of development of a future *micro*RNA product candidate, especially once a candidate has reached the stage of clinical development. For example, in our alliance with GSK, GSK has the option to obtain an exclusive worldwide license to develop, manufacture and commercialize product candidates upon the achievement of relevant efficacy and safety endpoints in the first clinical trial designed to show efficacy, safety and tolerability with respect to each of four potential programs or earlier, at GSK s option. However, GSK is not under any obligation to exercise its option to progress any of our *micro*RNA development candidates. While each of AstraZeneca, GSK and Sanofi have development obligations with respect to programs that they may elect to pursue under their respective agreements, our ability to ultimately recognize revenue from these relationships will depend upon the ability and willingness of our alliance partners to successfully meet their respective responsibilities under our agreements with them. Our ability to recognize revenues from successful strategic alliances may be impaired by several factors including:

- an alliance partner may shift its priorities and resources away from our programs due to a change in business strategies, or a merger, acquisition, sale or downsizing of its company or business unit;
- an alliance partner may cease development in therapeutic areas which are the subject of our strategic alliances;
- an alliance partner may change the success criteria for a particular program or potential product candidate thereby delaying or ceasing development of such program or candidate;
- a significant delay in initiation of certain development activities by an alliance partner will also delay payment of milestones tied to such activities, thereby impacting our ability to fund our own activities;
- an alliance partner could develop a product that competes, either directly or indirectly, with an alliance product;
- an alliance partner with commercialization obligations may not commit sufficient financial or human resources to the marketing, distribution or sale of a product;
- an alliance partner with manufacturing responsibilities may encounter regulatory, resource or quality issues and be unable to meet demand requirements;

an alliance partner may exercise its rights under the agreement to terminate a strategic alliance;

a dispute may arise between us and an alliance partner concerning the research, development or commercialization of a program or product candidate resulting in a delay in milestones, royalty

Table of Contents

payments or termination of a program and possibly resulting in costly litigation or arbitration which may divert management attention and resources; and

an alliance partner may use our proprietary information or intellectual property in such a way as to invite litigation from a third party or fail to maintain or prosecute intellectual property rights such that our rights in such property are jeopardized.

Specifically, with respect to termination rights, after expiration of an initial research term, Sanofi may terminate the entire alliance or any alliance target program for any or no reason upon 30 days written notice to us. The agreement with Sanofi may also be terminated by either party for material breach by the other party, including a failure to comply with such party s diligence obligations that remains uncured after 120 days. Similarly, GSK may terminate the entire alliance or any alliance target program for any or no reason upon 90 days written notice to us and the agreement may also be terminated by either party for material breach by the other party, including a failure to comply with such party s diligence obligations that remains uncured after a specified notice period. The agreement with AstraZeneca may be terminated by either party in the event of the other party s material breach which remains uncured after 40 business days following notice thereof (or 30 business days in the case of nonpayment). In addition, AstraZeneca may terminate the agreement in its entirety for any reason upon 60 business days written notice to us. Depending on the timing of any such termination, we may not be entitled to receive the option exercise fees or milestone payments, as these payments terminate with termination of the respective program or agreement.

If any of our alliance partners do not elect to pursue the development and commercialization of our *micro*RNA development candidates or if they terminate the strategic alliance, then, depending on the event:

in the case of Sanofi, under certain circumstances, we may owe Sanofi royalties with respect to product candidates covered by our agreement with Sanofi that we elect to continue to commercialize, depending upon the stage of development at which such product commercialization rights reverted back to us, or additional payments if we license such product candidates to third parties;

the development of our product candidates subject to the AstraZeneca agreement, GSK agreement or Sanofi agreement, as applicable, may be terminated or significantly delayed;

our cash expenditures could increase significantly if it is necessary for us to hire additional employees and allocate scarce resources to the development and commercialization of product candidates that were previously funded, or expected to be funded, by AstraZeneca, GSK or Sanofi, as applicable;

we would bear all of the risks and costs related to the further development and commercialization of product candidates that were previously the subject of the AstraZeneca agreement, GSK agreement or Sanofi agreement, as applicable, including the reimbursement of third parties; and

in order to fund further development and commercialization, we may need to seek out and establish alternative strategic alliances with third-party partners; this may not be possible, or we may not be able to do so on terms which are acceptable to us, in which case it may be necessary for us to limit the size or scope of one or more of our programs or increase our expenditures and seek additional funding by other means.

Any of these events would have a material adverse effect on our results of operations and financial condition.

We expect to rely on third parties to conduct some aspects of our compound formulation, research and preclinical testing, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such formulation, research or testing.

We do not expect to independently conduct all aspects of our drug discovery activities, compound formulation research or preclinical testing of product candidates. We currently rely and expect to continue to rely on third parties to conduct some aspects of our preclinical testing.

34

Table of Contents

Any of these third parties may terminate their engagements with us at any time. If we need to enter into alternative arrangements, it would delay our product development activities. Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibilities. For example, for product candidates that we develop and commercialize on our own, we will remain responsible for ensuring that each of our IND-enabling studies and clinical trials are conducted in accordance with the study plan and protocols for the trial.

If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our studies in accordance with regulatory requirements or our stated study plans and protocols, we will not be able to complete, or may be delayed in completing, the necessary preclinical studies to enable us or our strategic alliance partners to select viable product candidates for IND submissions and will not be able to, or may be delayed in our efforts to, successfully develop and commercialize such product candidates.

We intend to rely on third-party manufacturers to produce our preclinical supplies, and we intend to rely on third parties to produce clinical supplies of any product candidates that we advance into clinical trials and commercial supplies of any approved product candidates.

Reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured the product candidates ourselves, including:

- the inability to meet any product specifications and quality requirements consistently;
- a delay or inability to procure or expand sufficient manufacturing capacity;
- manufacturing and product quality issues related to scale-up of manufacturing;
- costs and validation of new equipment and facilities required for scale-up;
- a failure to comply with cGMP and similar foreign standards;
- the inability to negotiate manufacturing agreements with third parties under commercially reasonable terms;
- termination or nonrenewal of manufacturing agreements with third parties in a manner or at a time that is costly or damaging to us;
- the reliance on a limited number of sources, and in some cases, single sources for raw materials, such that if we are unable to secure a sufficient supply of these product components, we will be unable to manufacture and sell future product candidates in a timely fashion, in sufficient quantities or under acceptable terms;
- the lack of qualified backup suppliers for any raw materials that are currently purchased from a single source supplier;
- operations of our third-party manufacturers or suppliers could be disrupted by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or supplier;

carrier disruptions or increased costs that are beyond our control; and

the failure to deliver products under specified storage conditions and in a timely manner.

Any of these events could lead to clinical study delays or failure to obtain regulatory approval, or impact our ability to successfully commercialize future products. Some of these events could be the basis for FDA action, including injunction, recall, seizure or total or partial suspension of production.

Table of Contents

We expect to rely on limited sources of supply for the drug substance of future product candidates and any disruption in the chain of supply may cause a delay in developing and commercializing these product candidates.

We intend to establish manufacturing relationships with a limited number of suppliers to manufacture raw materials and the drug substance of any product candidate for which we are responsible for preclinical or clinical development. Each supplier may require licenses to manufacture such components if such processes are not owned by the supplier or in the public domain. As part of any marketing approval, a manufacturer and its processes are required to be qualified by the FDA prior to commercialization. If supply from the approved vendor is interrupted, there could be a significant disruption in commercial supply. An alternative vendor would need to be qualified through an NDA supplement which could result in further delay. The FDA or other regulatory agencies outside of the United States may also require additional studies if a new supplier is relied upon for commercial production. Switching vendors may involve substantial costs and is likely to result in a delay in our desired clinical and commercial timelines.

In addition, if our alliance partners elect to pursue the development and commercialization of certain programs, we will lose control over the manufacturing of the product candidate subject to the agreement. For example, if Sanofi elects to develop and commercialize a product candidate targeting miR-21 for HCC or kidney fibrosis under its strategic alliance with us, Sanofi will be responsible for the manufacture of the product candidates for clinical trials. Sanofi will be free to use a manufacturer of its own choosing or manufacture the product candidates in its own manufacturing facilities. In such a case, we will have no control over Sanofi s processes or supply chains to ensure the timely manufacture and supply of the product candidates. In addition, we will not be able to ensure that the product candidates will be manufactured under the correct conditions to permit the product candidates to be used in such clinical trials. Each of AstraZeneca and GSK will have similar obligations to manufacture product candidates which it takes into clinical trials under its strategic alliance with us and we will face similar risks as to those product candidates.

These factors could cause the delay of clinical trials, regulatory submissions, required approvals or commercialization of our future product candidates, cause us to incur higher costs and prevent us from commercializing our products successfully. Furthermore, if our suppliers fail to deliver the required commercial quantities of active pharmaceutical ingredients on a timely basis and at commercially reasonable prices, and we are unable to secure one or more replacement suppliers capable of production at a substantially equivalent cost, our clinical trials may be delayed or we could lose potential revenue.

Manufacturing issues may arise that could increase product and regulatory approval costs or delay commercialization.

As we scale-up manufacturing of future product candidates and conduct required stability testing, product, packaging, equipment and process-related issues may require refinement or resolution in order to proceed with any clinical trials and obtain regulatory approval for commercial marketing. We may identify significant impurities, which could result in increased scrutiny by the regulatory agencies, delays in clinical programs and regulatory approval, increases in our operating expenses, or failure to obtain or maintain approval for future product candidates or any approved products.

We expect to rely on third parties to conduct, supervise and monitor our clinical trials, and if those third parties perform in an unsatisfactory manner, it may harm our business.

If we or our strategic alliance partners commence clinical trials, we expect to rely on CROs and clinical trial sites to ensure the proper and timely conduct of our clinical trials. While we will have agreements governing their activities, we and our strategic alliance partners will have limited influence over their actual performance. We will control only certain aspects of our CROs activities. Nevertheless, we or our strategic alliance partners will be responsible for ensuring that each of our clinical trials is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards and our reliance on the CROs does not relieve us of our regulatory responsibilities.

Table of Contents

We, our alliance partners and our CROs are required to comply with the FDA s cGCPs for conducting, recording and reporting the results of IND-enabling studies and clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of clinical trial participants are protected. The FDA enforces these cGCPs through periodic inspections of trial sponsors, principal investigators and clinical trial sites. If we or our CROs fail to comply with applicable cGCPs, the clinical data generated in our future clinical trials may be deemed unreliable and the FDA may require us to perform additional clinical trials before approving any marketing applications. Upon inspection, the FDA may determine that our clinical trials did not comply with cGCPs. In addition, our future clinical trials will require a sufficiently large number of test subjects to evaluate the safety and effectiveness of a potential drug product. Accordingly, if our CROs fail to comply with these regulations or fail to recruit a sufficient number of patients, we may be required to repeat such clinical trials, which would delay the regulatory approval process.

Our CROs will not be our employees, and we will not be able to control whether or not they devote sufficient time and resources to our clinical and nonclinical programs. These CROs may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials, or other drug development activities which could harm our competitive position. If our CROs do not successfully carry out their contractual duties or obligations, fail to meet expected deadlines, or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements, or for any other reasons, our clinical trials may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for, or successfully commercialize our future product candidates. As a result, our financial results and the commercial prospects for such products and any future product candidates that we develop would be harmed, our costs could increase, and our ability to generate revenues could be delayed.

We also expect to rely on other third parties to store and distribute drug products for any clinical trials that we may conduct. Any performance failure on the part of our distributors could delay clinical development or marketing approval of our future product candidates or commercialization of our products, if approved, producing additional losses and depriving us of potential product revenue.

RISKS RELATED TO OUR INTELLECTUAL PROPERTY

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 compete effectively in our markets.

We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our future products and product candidates. The strength of patents in the biotechnology and pharmaceutical field involves complex legal and scientific questions and can be uncertain. The patent applications that we own or in-license may fail to result in issued patents with claims that cover the products in the United States or in other foreign countries. There is no assurance that all of the potentially relevant prior art relating to our patents and patent applications has been found, which can invalidate a patent or prevent a patent from issuing based on a pending patent application. Even if patents do successfully issue, third parties may challenge their validity, enforceability or scope, which may result in such patents being narrowed or invalidated. Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property or prevent others from designing around our claims.

If the patent applications we hold or have in-licensed with respect to our programs or product candidates fail to issue or if their breadth or strength of protection is threatened, it could dissuade companies from collaborating with us to develop product candidates, and threaten our ability to commercialize, future products. We cannot offer any assurances about which, if any, patents will issue or whether any issued patents will be found invalid and unenforceable or will be threatened by third parties. In particular, we are aware that Santaris Pharma A/S, or Santaris, has initiated reexamination of and filed oppositions to patents owned by Stanford University and

Table of Contents

licensed to us, in each case relating to miR-122, and has filed oppositions to a patent owned by us relating to miR-122 and to a patent owned by Isis relating to chemical modification of oligonucleotides. Any successful opposition to these patents or any other patents owned by or licensed to us could deprive us of rights necessary for the successful commercialization of any product candidates that we or our strategic alliance partners may develop. Further, if we encounter delays in regulatory approvals, the period of time during which we could market a product candidate under patent protection could be reduced. Since patent applications in the United States and most other countries are confidential for a period of time after filing, and some remain so until issued, we cannot be certain that we were the first to file any patent application related to a product candidate. Furthermore, if third parties have filed such patent applications, an interference proceeding in the United States can be initiated by a third party to determine who was the first to invent any of the subject matter covered by the patent claims of our applications. In addition, patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after it is filed. Various extensions may be available however the life of a patent, and the protection it affords, is limited. Once the patent life has expired for a product, we may be open to competition from generic medications.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable, processes for which patents are difficult to enforce and any other elements of our drug discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. Although we expect all of our employees to assign their inventions to us, and all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information or technology to enter into confidentiality agreements, we cannot provide any assurances that all such agreements have been duly executed or that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. In addition, others may independently discover our trade secrets and proprietary information. For example, the FDA, as part of its Transparency Initiative, is currently considering whether to make additional information publicly available on a routine basis, including information that we may consider to be trade secrets or other proprietary information, and it is not clear at the present time how the FDA s disclosure policies may change in the future, if at all.

Further, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the United States and abroad. If we are unable to prevent material disclosure of the non-patented intellectual property related to our technologies to third parties, and there is no guarantee that we will have any such enforceable trade secret protection, we may not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, results of operations and financial condition.

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, 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, or U.S. PTO, 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. 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

Table of Contents

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.

If we fail to comply with our obligations in the agreements under which we license intellectual property rights from third parties or otherwise experience disruptions to our business relationships with our licensors, we could lose license rights that are important to our business.

We are a party to a number of intellectual property license agreements that are important to our business and expect to enter into additional license agreements in the future. Our existing license agreements impose, and we expect that future license agreements will impose, various diligence, milestone payment, royalty and other obligations on us. For example, under our exclusive license agreement for Max-Planck-Innovation GmbH s proprietary technology and know-how covering *micro*RNA sequences, we are required to use commercially reasonable diligence to develop and commercialize a product and to satisfy specified payment obligations. If we fail to comply with our obligations under our agreement with Max-Planck-Innovation GmbH or our other license agreements, or we are subject to a bankruptcy, the licensor may have the right to terminate the license, in which event we, or our strategic alliance partners, would not be able to market products covered by the license. In addition, our exclusive license agreements with our founding companies, Alnylam and Isis, provide us with rights to nucleotide technologies in the field of *micro*RNA therapeutics based on oligonucleotides that modulate up-regulated *micro*RNAs. Some of these technologies, such as intellectual property relating to the chemical modification of oligonucleotides, are relevant to our product candidate development programs. If our license agreements with Alnylam or Isis are terminated, or our business relationships with either of these companies or our other licensors are disrupted by events that may include the acquisition of either company, our access to critical intellectual property rights will be materially and adversely affected.

We may need to obtain licenses from third parties to advance our research or allow commercialization of our future product candidates, and we have done so from time to time. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all. In that event, we would be unable to further develop and commercialize one or more of our future product candidates, which could harm our business significantly. We cannot provide any assurances that third-party patents do not exist which might be enforced against our future products, resulting in either an injunction prohibiting our sales, or, with respect to our sales, an obligation on our part to pay royalties and/or other forms of compensation to third parties.

Table of Contents

We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our patents or the patents of our licensors. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that a patent of ours or our licensors is not valid or is unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated or interpreted narrowly and could put our patent applications at risk of not issuing.

Interference proceedings provoked by third parties or brought by us may be necessary to determine the priority of inventions with respect to our patents or patent applications or those of our alliance partners or licensors. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Our defense of litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. We may not be able to prevent, alone or with our licensors, misappropriation of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the United States.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our common stock.

We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties.

We employ individuals who were previously employed at other biotechnology or pharmaceutical companies. We may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed confidential information of our employees former employers or other third parties. We may also be subject to claims that former employers or other third parties have an ownership interest in our patents. Litigation may be necessary to defend against these claims. There is no guarantee of success in defending these claims, and if we are successful, litigation could result in substantial cost and be a distraction to our management and other employees.

RISKS RELATED TO COMMERCIALIZATION OF PRODUCT CANDIDATES

The commercial success of our miR-21, miR-122 and miR-33 programs, which are part of our strategic alliance agreements with Sanofi, GSK and AstraZeneca, respectively, will depend in large part on the development and marketing efforts of our alliance partners. If our alliance partners are unable to perform in accordance with the terms of our agreements, our potential to generate future revenue from these programs would be significantly reduced and our business would be materially and adversely harmed.

If any of Sanofi, GSK or AstraZeneca elects to pursue the development and commercialization of any of the *micro*RNA product candidates that are subject to their respective strategic alliance agreements with us, we will have limited influence and/or control over their approaches to development and commercialization. If Sanofi, GSK, AstraZeneca or any potential future strategic alliance partners do not perform in the manner that we expect or fail to fulfill their responsibilities in a timely manner, or at all, the clinical development, regulatory approval and commercialization efforts related to product candidates we have licensed to such strategic alliance partners could be delayed or terminated. If we terminate any of our strategic alliances or any program thereunder due to a

Table of Contents

material breach by Sanofi, GSK or AstraZeneca, we have the right to assume the responsibility at our own expense for the development of the applicable *micro*RNA product candidates. Assuming sole responsibility for further development will increase our expenditures, and may mean we will need to limit the size and scope of one or more of our programs, seek additional funding and/or choose to stop work altogether on one or more of the affected product candidates. This could result in a limited potential to generate future revenue from such *micro*RNA product candidates and our business could be materially and adversely affected. Further, under certain circumstances, we may owe Sanofi, GSK or AstraZeneca, as applicable, royalties on any product candidate that we may successfully commercialize.

We face significant competition from other biotechnology and pharmaceutical companies and our operating results will suffer if we fail to compete effectively.

The biotechnology and pharmaceutical industries are intensely competitive. We have competitors both in the United States and internationally, including major multinational pharmaceutical companies, biotechnology companies and universities and other research institutions. We are aware of several companies that are working specifically to develop *micro*RNA therapeutics including Groove Biopharma, Inc., miRagen Therapeutics, Inc., Mirna Therapeutics, Inc., and Santaris. Many of our competitors have substantially greater financial, technical and other resources, such as larger research and development staff and experienced marketing and manufacturing organizations. Additional mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors may succeed in developing, acquiring or licensing on an exclusive basis, drug products that are more effective or less costly than any product candidate that we may develop.

All of our programs are in a preclinical development stage and are targeted toward indications for which there are approved products on the market or product candidates in clinical development. We will face competition from other drugs currently approved or that will be approved in the future for the same therapeutic indications. Our ability to compete successfully will depend largely on our ability to leverage our experience in drug discovery and development to:

- discover and develop therapeutics that are superior to other products in the market;
- attract qualified scientific, product development and commercial personnel;
- obtain patent and/or other proprietary protection for our *micro*RNA product platform and future product candidates;
- obtain required regulatory approvals; and
- successfully collaborate with pharmaceutical companies in the discovery, development and commercialization of new therapeutics.

The availability of our competitors products could limit the demand, and the price we are able to charge, for any products that we may develop and commercialize. We will not achieve our business plan if the acceptance of any of these products is inhibited by price competition or the reluctance of physicians to switch from existing drug products to our products, or if physicians switch to other new drug products or choose to reserve our future products for use in limited circumstances. The inability to compete with existing or subsequently introduced drug products would have a material adverse impact on our business, financial condition and prospects.

Established pharmaceutical companies may invest heavily to accelerate discovery and development of novel compounds or to in-license novel compounds that could make our future product candidates less competitive. In addition, any new product that competes with an approved product must demonstrate compelling advantages in efficacy, convenience, tolerability and safety in order to overcome price competition and to be commercially

Table of Contents

successful. Accordingly, our competitors may succeed in obtaining patent protection, receiving FDA approval or discovering, developing and commercializing product candidates before we do, which would have a material adverse impact on our business.

The commercial success of our product candidates will depend upon the acceptance of these product candidates by the medical community, including physicians, patients and healthcare payors.

The degree of market acceptance of any product candidates will depend on a number of factors, including:

- demonstration of clinical safety and efficacy compared to other products;
- the relative convenience, ease of administration and acceptance by physicians, patients and healthcare payors;
- the prevalence and severity of any AEs;
- limitations or warnings contained in the FDA-approved label for such products;
- availability of alternative treatments;
- pricing and cost-effectiveness;
- the effectiveness of our or any collaborators sales and marketing strategies;
- our ability to obtain hospital formulary approval;
- our ability to obtain and maintain sufficient third party coverage or reimbursement; and
- the willingness of patients to pay out-of-pocket in the absence of third party coverage.

Unless other formulations are developed in the future, we expect our compounds to be formulated in an injectable form. Injectable medications may be disfavored by patients or their physicians in the event drugs which are easy to administer, such as oral medications, are available. If a product is approved, but does not achieve an adequate level of acceptance by physicians, patients and healthcare payors, we may not generate sufficient revenues from such product and we may not become or remain profitable.

If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to market and sell our future product candidates, we may be unable to generate any revenues.

We currently do not have an organization for the sales, marketing and distribution of pharmaceutical products and the cost of establishing and maintaining such an organization may exceed the cost-effectiveness of doing so. In order to market any products that may be approved, we must build our sales, marketing, managerial and other non-technical capabilities or make arrangements with third parties to perform these services. With respect to our current programs which are the subject of existing strategic alliances, such as miR-21 with Sanofi, miR-122 with GSK and miR-33 with AstraZeneca, we intend to rely completely on our alliance partner for sales and marketing. In addition, we intend to enter into strategic alliances with third parties to commercialize other future product candidates, including in markets outside of the United States or for other large markets that are beyond our resources. Although we intend to establish a sales organization if we are able to obtain approval to

market any product candidates for niche markets in the United States, we will also consider the option to enter into strategic alliances for future product candidates in the United States if commercialization requirements exceed our available resources. This will reduce the revenue generated from the sales of these products.

Our current and future strategic alliance partners, if any, may not dedicate sufficient resources to the commercialization of our future product candidates or may otherwise fail in their commercialization due to factors beyond our control. If we are unable to establish effective alliances to enable the sale of our future product candidates to healthcare professionals and in geographical regions, including the United States, that will

Table of Contents

not be covered by our own marketing and sales force, or if our potential future strategic alliance partners do not successfully commercialize the product candidates, our ability to generate revenues from product sales will be adversely affected.

If we are unable to establish adequate sales, marketing and distribution capabilities, whether independently or with third parties, we may not be able to generate sufficient product revenue and may not become profitable. We will be competing with many companies that currently have extensive and well-funded marketing and sales operations. Without an internal team or the support of a third party to perform marketing and sales functions, we may be unable to compete successfully against these more established companies.

If we obtain approval to commercialize any approved products outside of the United States, a variety of risks associated with international operations could materially adversely affect our business.

Our strategic alliance agreements with Sanofi, GSK and AstraZeneca provide that our partners will be responsible for the commercialization of future product candidates, if any, from our miR-21, miR-122 and miR-33 programs, as applicable. If any other future product candidates that we may develop are approved for commercialization, we may also enter into agreements with third parties to market them on a worldwide basis or in more limited geographical regions. We expect that we will be subject to additional risks related to entering into international business relationships, including:

- different regulatory requirements for drug approvals in foreign countries;
- reduced protection for intellectual property rights;
- unexpected changes in tariffs, trade barriers and regulatory requirements;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign taxes, including withholding of payroll taxes;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geopolitical actions, including war and terrorism, or natural disasters including earthquakes, typhoons, floods and fires.

Coverage and adequate reimbursement may not be available for our future product candidates, which could make it difficult for us to sell products profitably.

Market acceptance and sales of any future product candidates that we develop will depend on coverage and reimbursement policies and may be affected by future healthcare reform measures. Government authorities and third party payors, such as private health insurers, hospitals and health maintenance organizations, decide which drugs they will pay for and establish reimbursement levels. We cannot be sure that coverage and adequate reimbursement will be

Table of Contents

available for any future product candidates. Also, inadequate reimbursement amounts may reduce the demand for, or the price of, our future products. If reimbursement is not available, or is available only at limited levels, we may not be able to successfully commercialize future product candidates that we develop.

In addition, we cannot be certain if and when we will obtain formulary approval to allow us to sell any products that we may develop and commercialize into our target markets. Obtaining formulary approval from hospitals and from payers can be an expensive and time consuming process. Failure to obtain timely formulary approval will limit our commercial success.

There have been a number of legislative and regulatory proposals to change the healthcare system in the United States and in some foreign jurisdictions that could affect our ability to sell products profitably. These legislative and/or regulatory changes may negatively impact the reimbursement for drug products, following approval. The availability of numerous generic treatments may also substantially reduce the likelihood of reimbursement for our future products. The potential application of user fees to generic drug products may expedite the approval of additional generic drug treatments. We expect to experience pricing pressures in connection with the sale of any products that we develop, due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative changes. If we fail to successfully secure and maintain reimbursement coverage for our future products or are significantly delayed in doing so, we will have difficulty achieving market acceptance of our future products and our business will be harmed.

In addition, in some non-US jurisdictions, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. For example, the EU provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products. Historically, products launched in the EU do not follow price structures of the US and generally tend to be priced significantly lower.

RISKS RELATED TO OUR BUSINESS OPERATIONS AND INDUSTRY

Our future success depends on our ability to retain key executives and to attract, retain and motivate qualified personnel.

We are highly dependent on principal members of our executive team, the loss of whose services may adversely impact the achievement of our objectives. While we have entered into employment agreements with each of our executive officers, any of them could leave our employment at any time, as all of our employees are at will employees. Recruiting and retaining other qualified employees for our business, including scientific and technical personnel, will also be critical to our success. There is currently a shortage of skilled executives in our industry, which is likely to continue. As a result, competition for skilled personnel is intense and the turnover rate can be high. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical companies for individuals with similar skill sets. In addition, failure to succeed in preclinical studies and clinical trials may make it more challenging to recruit and retain qualified personnel. The inability to recruit or loss of the services of any executive or key employee might impede the progress of our research, development and commercialization objectives.

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

As of December 31, 2012, we had 66 full-time employees. As our company matures, we expect to expand our employee base to increase our managerial, scientific and operational, commercial, financial and other

Table of Contents

resources and to hire more consultants and contractors. Future growth would impose significant additional responsibilities on our management, including the need to identify, recruit, maintain, motivate and integrate additional employees, consultants and contractors. Also, our management may need to divert a disproportionate amount of its attention away from our day-to-day activities and devote a substantial amount of time to managing these growth activities. We may not be able to effectively manage the expansion of our operations, which may result in weaknesses in our infrastructure, give rise to operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could require significant capital expenditures and may divert financial resources from other projects, such as the development of additional product candidates. If our management is unable to effectively manage our growth, our expenses may increase more than expected, our ability to generate and/or grow revenues could be reduced, and we may not be able to implement our business strategy. Our future financial performance and our ability to commercialize future product candidates and compete effectively will depend, in part, on our ability to effectively manage any future growth.

Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements and insider trading.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with the regulations of the FDA and non-U.S. regulators, provide accurate information to the FDA and non-U.S. regulators, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and cause serious harm to our reputation. We have adopted a code of conduct, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

Any future relationships with customers and third party payors may be subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, false claims laws and health information privacy and security laws. If we are unable to comply, or have not fully complied, with such laws, we could face criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

If we obtain FDA approval for any of our product candidates and begin commercializing those products in the US, our operations may be directly, or indirectly through our customers, subject to various federal and state fraud and abuse laws, including, without limitation, the federal Anti-Kickback Statute and the federal False Claims Act. These laws may impact, among other things, our proposed sales, marketing and education programs. In addition, we may be subject to patient privacy regulation by the federal government and by the U.S. states and foreign jurisdictions in which we conduct our business. The laws that may affect our ability to operate include:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, to induce, or in return for, either the referral of an individual, or the purchase or recommendation of an item or service for which payment may be made under a federal healthcare program, such as the Medicare and Medicaid programs;

Table of Contents

federal civil and criminal false claims laws and civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third party payers that are false or fraudulent;

the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit executing a scheme to defraud any healthcare benefit program and making false statements relating to healthcare matters;

HIPAA, as amended by the Health Information Technology and Clinical Health Act of 2009, or HITECH, and its implementing regulations, which imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information; and

state and foreign law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third party payer, including commercial insurers, and state and foreign laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

If our operations are found to be in violation of any of the laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including, without limitation, civil and criminal penalties, damages, fines, possible exclusion from Medicare, Medicaid and other government healthcare programs, and curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

We face potential product liability, and, if successful claims are brought against us, we may incur substantial liability and costs.

The use of our future product candidates in clinical trials and the sale of any products for which we obtain marketing approval exposes us to the risk of product liability claims. Product liability claims might be brought against us by consumers, healthcare providers, pharmaceutical companies or others selling or otherwise coming into contact with our products. Certain oligonucleotide therapeutics have shown injection site reactions and pro-inflammatory effects and may also lead to impairment of kidney or liver function. There is a risk that our future product candidates may induce similar adverse events. If we cannot successfully defend against product liability claims, we could incur substantial liability and costs. In addition, regardless of merit or eventual outcome, product liability claims may result in:

impairment of our business reputation;

withdrawal of clinical trial participants;

costs due to related litigation;

distraction of management s attention from our primary business;

substantial monetary awards to patients or other claimants;

the inability to commercialize our future product candidates; and

decreased demand for our future product candidates, if approved for commercial sale.

We do not currently have any product liability insurance coverage. We anticipate obtaining such insurance prior to the commencement of any clinical trials but any such insurance coverage that we obtain may not be sufficient to reimburse us for any expenses or losses we may suffer. Moreover, insurance coverage is becoming increasingly expensive and in the future we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. If and when we obtain marketing approval for future product candidates, we intend to expand our insurance coverage to include the sale of commercial products; however, we may be unable to obtain product liability insurance on commercially reasonable terms or

Table of Contents

in adequate amounts. On occasion, large judgments have been awarded in class action lawsuits based on drugs that had unanticipated adverse effects. A successful product liability claim or series of claims brought against us could cause our stock price to decline and, if judgments exceed our insurance coverage, could adversely affect our results of operations and business.

Business interruptions could delay us in the process of developing our future products.

Our headquarters are located in San Diego County. We are vulnerable to natural disasters such as earthquakes and wild fires, as well as other events that could disrupt our operations. We do not carry insurance for earthquakes or other natural disasters and we may not carry sufficient business interruption insurance to compensate us for losses that may occur. Any losses or damages we incur could have a material adverse effect on our business operations.

RISKS RELATED TO OUR COMMON STOCK

Our stock price may be volatile.

Prior to our recently completed initial public offering, there was no public market for our common stock. The trading price of our common stock is likely to be volatile for the foreseeable future. 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 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;

the perception of the pharmaceutical industry by the public, legislatures, regulators and the investment community;

announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us, our strategic alliance partners or our competitors;

disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;

additions or departures of key scientific or management personnel;

significant lawsuits, including patent or stockholder litigation;

Table of Contents

changes in the market valuations of similar companies;

sales of our common stock by us or our stockholders in the future; and

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.

As of December 31, 2012, our executive officers, directors, 5% stockholders and their affiliates beneficially own approximately 82% of our outstanding voting stock. Therefore, 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.

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 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 for up to five years, 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 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 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.

Table of Contents

The requirements of being a public company may strain our resources and divert management s attention.

As a public company, we have incurred, and will continue to incur, significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act, as well as rules subsequently implemented by the Securities and Exchange Commission, or SEC, and The NASDAQ Global Market have imposed various requirements on public companies. In July 2010, the Dodd-Frank Wall Street Reform and Consumer Protection Act, or the Dodd-Frank Act, was enacted. There are significant corporate governance and executive compensation related provisions in the Dodd-Frank Act that require the SEC to adopt additional rules and regulations in these areas such as say on pay and proxy access. Recent legislation permits smaller emerging growth companies to implement many of these requirements over a longer period and up to five years from the pricing of our initial public offering. We intend to take advantage of this new legislation but cannot guarantee that we will not be required to implement these requirements sooner than budgeted or planned and thereby incur unexpected expenses. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which may lead to additional compliance costs and impact the manner in which we operate our business in ways we cannot currently anticipate. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs and will make some activities more time-consuming and costly. For example, we expect these rules and regulations to make it more difficult and more expensive for us to obtain director and officer liability insurance and we may be required to incur substantial costs to maintain our current levels of such coverage.

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, executive management team, holders of our convertible preferred stock, holders of our convertible notes and our strategic partners, including each of our founding companies, Alnylam and Isis, and each of AstraZeneca, GSK and Sanofi, have agreed that for a period of 365 days after the date of our final prospectus for our initial public offering dated October 4, 2012, 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. Substantially all of our other stockholders and option holders have agreed to similar obligations for a period of 180 days after the date of our final prospectus for our initial public offering dated October 4, 2012. Subject to certain limitations, approximately 26,902,076 shares will become eligible for sale upon expiration of the lock-up period. 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.

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.

Table of Contents

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.

Pursuant to our 2012 Equity Incentive Plan which became effective upon the closing of our initial public offering, 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. Currently, we plan to register the increased number of shares available for issuance under the 2012 plan each year. If our board of directors elects to increase the number of shares available for future grant by the maximum amount each year, our stockholders may experience additional dilution, which could cause our stock price to fall.

We could be subject to securities class action litigation.

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because pharmaceutical companies have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management s attention and resources, which could harm our business.

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.

Provisions in our amended and restated certificate of incorporation and bylaws, as well as provisions of Delaware law, could make it more difficult for a third party to acquire us or increase the cost of acquiring us, even if doing so would benefit our stockholders or remove our current management.

Some provisions of our charter documents and Delaware law may have anti-takeover effects that could discourage an acquisition of us by others, even if an acquisition would be beneficial to our stockholders and may prevent attempts by our stockholders to replace or remove our current management. These provisions include:

Table of Contents

authorizing the issuance of blank check preferred stock, the terms of which may be established and shares of which may be issued without stockholder approval;

limiting the removal of directors by the stockholders;

prohibiting stockholder action by written consent, thereby requiring all stockholder actions to be taken at a meeting of our stockholders;

eliminating the ability of stockholders to call a special meeting of stockholders; and

establishing advance notice requirements for nominations for election to the board of directors or for proposing matters that can be acted upon at stockholder meetings.

In addition, we are subject to Section 203 of the Delaware General Corporation Law, which generally prohibits a Delaware corporation from engaging in any of a broad range of business combinations with an interested stockholder for a period of three years following the date on which the stockholder became an interested stockholder, unless such transactions are approved by our board of directors. This provision could have the effect of delaying or preventing a change in control, whether or not it is desired by or beneficial to our stockholders. Further, other provisions of Delaware law may also discourage, delay or prevent someone from acquiring us or merging with us.

Item 1B. Unresolved Staff Comments.

Not applicable.

Item 2. Properties.

Our administrative offices and research laboratory is located in La Jolla, California. As of December 31, 2012, we had a lease for approximately 22,000 square feet for office and laboratory space. Our lease currently expires in June 2017, subject to our option to renew for up to two additional three-year terms. In November 2012, we amended our lease to expand our laboratory and office space by approximately 7,000 square feet, effective May 2013, including the addition of an approximately 3,135 square foot dedicated research and development laboratory. We believe that our facility is sufficient to meet our needs and that suitable additional space will be available as and when needed.

Item 3. Legal Proceedings.

None.

Item 4. Mine Safety Disclosures.

Not applicable.

Table of Contents

PART II

Item 5. Market for Registrant s Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Market Information

Our common stock began trading on The NASDAQ Global Market on October 4, 2012 under the symbol RGLS. Prior to such time, there was no public market for our common stock. The following table sets forth the high and low sales prices per share of our common stock as reported on The NASDAQ Global Market for the period indicated.

	Price Range	
	High	Low
Year Ended December 31, 2012		
Fourth Quarter (commencing October 4, 2012)	$ 6.49	$ 4.02

Holders of Record

As of February 14, 2013, there were approximately 28 holders of record of our common stock.

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.

Securities Authorized for Issuance Under Equity Compensation Plans

Information about our equity compensation plans is incorporated herein by reference to Item 12 of Part III of this Annual Report.

Table of Contents

Performance Graph

The following graph shows a comparison from October 4, 2012 (the date our common stock commenced trading on The NASDAQ Global Market) through December 31, 2012 of the cumulative total return for our common stock, the NASDAQ Biotechnology Index (NBI) and the NASDAQ Composite Index (CCMP). The graph assumes an initial investment of $100 on October 4, 2012. The comparisons in the graph are not intended to forecast or be indicative of possible future performance of our common stock.

Recent Sales of Unregistered Securities

During the fiscal year ended December 31, 2012, we issued and sold the following unregistered securities (excluding those previously disclosed in a Quarterly Report on Form 10-Q or in a Current Report on Form 8-K):

From January 1, 2012 to June 30, 2012, we granted stock options under our 2009 equity incentive plan to purchase 562,148 shares of common stock to our employees, directors and consultants, having an exercise price of $2.66 per share. In addition, options to purchase 90,210 shares of common stock have been exercised through June 30, 2012 for aggregate consideration of approximately $34,000, at an average exercise price of $0.38 per share.

The sales and issuances of securities in the transactions described above were deemed to be exempt from registration under the Securities Act in reliance upon Rule 701 promulgated under Section 3(b) of the Securities Act as transactions pursuant to compensatory benefit plans and contracts relating to compensation as provided under Rule 701. The recipients of securities in each transaction represented their intentions to acquire the securities for investment only and not with a view to or for sale in connection with any distribution thereof and appropriate legends were affixed to the securities issued in these transactions. All recipients had adequate access, through employment or other relationships, to information about us. All certificates representing the securities issued in these transactions included appropriate legends setting forth that the securities had not been offered or sold pursuant to a registration statement and describing the applicable restrictions on transfer of the securities.

Use of Proceeds

On October 4, 2012, we commenced our initial public offering pursuant to a registration statement on Form S-1 (File No. 333-183384) that was declared effective by the SEC on October 4, 2012 and that registered an aggregate of 12,937,500 shares of our common stock for sale to the public at a price of $4.00 per share and an

Table of Contents

aggregate offering price of $51,750,000. On October 10, 2012 and October 23, 2012, we sold 11,250,000 shares and 1,480,982 shares of our common stock, respectively, to the public at a price of $4.00 per share for an aggregate gross offering price of $50,923,928. The net offering proceeds to us, after deducting underwriting discounts and commissions and offering costs, were approximately $44.9 million. Concurrently with the completion of our initial public offering, we sold 6,250,000 shares of common stock in a private placement to AstraZeneca at the initial public offering price of $4.00 per share, resulting in net proceeds to the Company of $25.0 million.

We intend to use the net proceeds of our initial public offering and the concurrent private placement for preclinical and clinical development of our 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, including costs and expenses associated with being a public company. 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 our initial public offering and the concurrent private placement and could spend the proceeds in ways that do not improve our results of operations or enhance the value of our stock. As of December 31, 2012, we have invested the net proceeds from our initial public offering and the concurrent private placement in short- and intermediate-term, interest-bearing obligations, investment-grade instruments, certificates of deposit or direct or guaranteed obligations of the U.S. government.

Table of Contents

Item 6. Selected Financial Data.

The selected financial data set forth below is derived from our audited financial statements and may not be indicative of future operating results. The following selected financial data should be read in conjunction with the financial statements and notes thereto and Item 7, Management s Discussion and Analysis of Financial Condition and Results of Operations included elsewhere in this Annual Report. 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. Amounts are in thousands, except share and per share data.

	Year ended December 31,		
Statement of operations data	**2012**	**2011**	**2010**
Revenues:			
Revenue under strategic alliances	$ 12,700	$ 13,767	$ 8,112
Grant revenue		22	489
Total revenues	12,700	13,789	8,601
Operating expenses:			
Research and development	20,342	17,289	20,178
General and administrative	4,932	3,637	3,921
Total operating expenses	25,274	20,926	24,099
Loss from operations	(12,574)	(7,137)	(15,498)
Loss on extinguishment of debt	(1,738)		
Loss from change in value of convertible note payable	(2,969)		
Interest and other expense, net	(137)	(259)	(91)
Loss before income taxes	(17,418)	(7,396)	(15,589)
Income tax (benefit) expense	(10)	206	(30)
Net loss	$ (17,408)	(7,602)	$ (15,559)
Net loss per share, basic and diluted[(1)]	$ (2.12)	(85.82)	
Shares used to compute basic and diluted net loss per share[(1)]	8,212,538	88,582	

(1) See Note 2 of our Notes to Financial Statements appearing elsewhere in this Annual Report 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.

	As of December 31,		
Balance sheet data	**2012**	**2011**	**2010**
Cash, cash equivalents and short-term investments	$ 98,100	$ 38,144	$ 54,789
Working capital	86,161	25,816	40,446
Total assets	103,518	42,881	59,703
Convertible notes payable	10,134	10,815	11,227
Convertible preferred stock		42,691	42,691
Accumulated deficit	(60,419)	(43,011)	(35,409)
Total stockholders equity (deficit)	62,093	(41,494)	(34,695)

Item 7. Management s Discussion and Analysis of Financial Condition and Results of Operations.

You should read the following discussion and analysis together with Item 6. Selected Financial Data and our financial statements and related notes included elsewhere in this Annual Report. The following discussion contains forward-looking statements that involve risks and uncertainties. Our actual results could differ materially from those expressed or implied in any forward-looking statements as a result of various factors, including those set forth under the caption Item 1A. Risk Factors.

Table of Contents

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. *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 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 five distinct programs both independently and with our strategic alliance partners, GlaxoSmithKline plc, or GSK, Sanofi and AstraZeneca AB, or AstraZeneca. We anticipate that we will nominate at least two clinical development candidates in 2013 and file two INDs, with the U.S. Food and Drug Administration, or FDA, in 2014.

In April 2008, we entered into a product development and commercialization agreement with GSK. Under the terms of the agreement, we agreed to develop four programs of interest to GSK in the areas of inflammation and immunology and granted GSK an option to obtain an exclusive worldwide license to develop, manufacture and commercialize products in each program. We are responsible for the discovery, optimization and development of anti-miR product candidates in each program through proof-of-concept, defined as the achievement of relevant efficacy and safety endpoints in the first clinical trial designed to show efficacy, safety and tolerability, unless GSK chooses to exercise its option at an earlier stage. Upon entering into the agreement, we received an upfront payment of $15.0 million as an option fee, and GSK loaned $5.0 million to us under a convertible note. In connection with the expansion of the alliance to include miR-122 for the treatment of hepatitis C virus infection, or HCV, in February 2010, GSK made an upfront payment to us of $3.0 million and loaned an additional $5.0 million to us pursuant to a second convertible note. We are eligible to receive up to $144.5 million in preclinical, clinical, regulatory and commercialization milestone payments for each of the four *micro*RNA programs under our alliance with GSK. We are also eligible to receive tiered royalties as a percentage of annual sales which can increase up to the low end of the 10 to 20% range. These royalties are subject to reduction upon the expiration of certain patents or introduction of generic competition into the market, or if GSK is required to obtain licenses from third parties to develop or commercialize products under the alliance. Under our strategic alliance with GSK, we earned a $500,000 milestone payment in each of May 2009 and July 2011.

In June 2010, we entered into a collaboration and license agreement with Sanofi, which we subsequently amended, restated and superseded in July 2012. Under the terms of the agreement, we have agreed to collaborate with Sanofi to develop and commercialize licensed compounds targeting four *micro*RNA alliance targets initially focused in the field of fibrosis and have granted Sanofi an exclusive license to develop and commercialize products under the alliance. The agreement specified that miR-21 would be the first *micro*RNA alliance target in the field of fibrosis. Under the terms of the agreement, we received an upfront payment of $25.0 million, which was allocated to the research programs. In addition, Sanofi purchased $10.0 million of our series B convertible preferred stock. We also received $5.0 million for one year of research and development funding. Subsequently, we received a $5.0 million payment for research and development funding following each of the first and second anniversaries of our entry into the agreement in June 2010. We may be entitled to receive additional annual payments under the agreement to support our work on the research plan. We are also entitled to receive preclinical, clinical, regulatory and commercialization milestone payments of up to $640.0 million in the aggregate for all alliance product candidates. We are also entitled to receive royalties based on a percentage of net sales which will range from the mid-single digits to the low end of the 10 to 20% range, depending upon the target and the volume of sales. In August 2012, we entered into a collaboration and license agreement with AstraZeneca. Under the terms of the agreement, we agreed to collaborate with AstraZeneca to identify, research

Table of Contents

and develop licensed compounds targeting three *micro*RNA alliance targets in the fields of cardiovascular diseases, metabolic diseases and oncology and granted to AstraZeneca an exclusive, worldwide license to thereafter develop, manufacture and commercialize lead compounds designated by AstraZeneca in the course of the collaboration activities against the *micro*RNA alliance targets for all human therapeutic uses. We are responsible for discovery, optimization and development of anti-miR product candidates in each program until the acceptance of an IND or the end of the research term, which extends until the fourth anniversary of the date of the agreement, and may be extended upon mutual written agreement. Following the earlier to occur of the acceptance of an IND in a major market or the end of the research term, AstraZeneca will assume all costs, responsibilities and obligations for further development, manufacture and commercialization of alliance product candidates. Upon entering into the agreement, we became entitled to receive an upfront payment of $3.0 million. We are also entitled to receive preclinical, clinical and commercialization milestone payments of up to $509.0 million in the aggregate for all alliance product candidates. In addition, we are entitled to receive royalties based on a percentage of net sales which will range from the mid-single digits to the low end of the 10 to 20% range, depending upon the product and the volume of sales, which royalties may be reduced in certain limited circumstances. In August 2012 and in conjunction with the agreement, we entered into a Common Stock Purchase Agreement with AstraZeneca, pursuant to which we agreed to sell to AstraZeneca an aggregate of $25.0 million of common stock in a concurrent private placement with our initial public offering, at a price per share equal to that which all common stock was sold to the public in such initial public offering. In October 2012, in accordance with the Common Stock Purchase Agreement, we sold AstraZeneca 6,250,000 shares of common stock at a price per share of $4.00.

On October 10, 2012, we completed our initial public offering whereby we issued and sold 11,250,000 shares of common stock at a public offering price of $4.00 per share, resulting in net proceeds to the Company of approximately $39.5 million. Concurrently with the completion of our initial public offering on October 10, 2012, $5.0 million of outstanding principal plus accrued interest of $788,000 underlying a convertible note that we issued to GSK in April 2008 and amended and restated in July 2012, together with $5.0 million of outstanding principal plus accrued interest of $25,000 underlying a convertible note that we issued to Biogen Idec in August 2012, was automatically converted upon the closing of our initial public offering into an aggregate of 2,703,269 shares of our common stock. Upon the closing of our initial public offering, all shares of our outstanding convertible preferred stock automatically converted into an aggregate of 13,699,999 shares of common stock. On October 23, 2012, the underwriters for our initial public offering partially exercised an over-allotment option to purchase 1,480,982 shares of our common stock at $4.00 per share, resulting in net proceeds to us of approximately $5.5 million.

We have devoted substantial resources to developing our *micro*RNA product platform, protecting and enhancing our intellectual property estate and providing general and administrative support for these activities. We have not generated any revenue from product sales and, to date, have funded our operations primarily through upfront payments from our strategic alliances, the private placement of convertible preferred stock, convertible debt, government grants and our initial public offering. From inception in September 2007 through December 31, 2012, we raised a total of $190.4 million, including:

- $65.4 million principally from upfront payments from our strategic alliances, preclinical milestones, research funding and government grants;
- $30.0 million from the sale of equity securities to our founding companies;
- $50.0 million from the sale of equity and convertible debt securities to our strategic alliance partners; and
- $45.0 million from the sale of common stock through our initial public offering, net of offering costs of $5.9 million.

We have incurred losses in each year since our inception in September 2007. Our net losses were $17.4 million, $7.6 million and $15.5 million for the years ended December 31, 2012, 2011 and 2010, respectively. As

Table of Contents

of December 31, 2012, we had an accumulated deficit of $60.4 million. Substantially all of our operating losses resulted from expenses incurred in connection with our research programs and from general and administrative costs associated with our operations.

We expect to continue to incur significant expenses and increasing operating losses for at least the next several years. We anticipate that our expenses will increase substantially as we:

- select our clinical development candidates and initiate clinical trials;
- seek regulatory approvals for our product candidates that successfully complete clinical trials;
- maintain, expand and protect our intellectual property portfolio;
- continue our other research and development efforts;
- hire additional clinical, quality control, scientific, operational, financial and management personnel; and
- add operational, financial and management information systems.

Financial Operations Overview

Revenues

Our revenues generally consist of upfront payments for licenses or options to obtain licenses in the future, research and development funding and milestone payments under strategic alliance agreements, as well as funding received under government grants.

In the future, we may generate revenue from a combination of license fees and other upfront payments, research and development payments, milestone payments, product sales and royalties in connection with strategic alliances. We expect that any revenue we generate will fluctuate from quarter-to-quarter as a result of the timing of our achievement of preclinical, clinical, regulatory and commercialization milestones, if at all, the timing and amount of payments relating to such milestones and the extent to which any of our products are approved and successfully commercialized by us or our strategic alliance partners. If our strategic alliance partners do not elect or otherwise agree to fund our development costs pursuant to our strategic alliance agreements, or we or our strategic alliance partners fail to develop product candidates in a timely manner or obtain regulatory approval for them, our ability to generate future revenues, and our results of operations and financial position would be adversely affected.

Research and development expenses

Research and development expenses consist of costs associated with our research activities, including our drug discovery efforts, the preclinical development of our therapeutic programs, and our *micro*RNA biomarker program. Our research and development expenses include:

- employee-related expenses, including salaries, benefits, travel and stock-based compensation expense;
- external research and development expenses incurred under arrangements with third parties, such as contract research organizations, or CROs, consultants and our scientific advisory board;

license and sublicense fees; and

facilities, depreciation and other allocated expenses, which include direct and allocated expenses for rent and maintenance of facilities, depreciation of leasehold improvements and equipment, and laboratory and other supplies.

We expense research and development costs as incurred. We account for nonrefundable advance payments for goods and services that will be used in future research and development activities as expenses when the service has been performed or when the goods have been received.

Table of Contents

To date, we have conducted research on many different *micro*RNAs with the goal of understanding how they function and identifying those that might be targets for therapeutic modulation. At any given time we are working on multiple targets, primarily within our five therapeutic areas of focus. Our organization is structured to allow the rapid deployment and shifting of resources to focus on the best targets based on our ongoing research. As a result, in the early phase of our development, our research and development costs are not tied to any specific target. However, we are currently spending the vast majority of our research and development resources on our lead development programs.

Since our inception in January 2009, we have grown from 15 research and development personnel to 52 and have spent a total of approximately $66.8 million in research and development expenses through December 31, 2012.

We expect our research and development expenses to increase for the foreseeable future as we advance our research programs toward the clinic and initiate clinical trials. The process of conducting preclinical studies and clinical trials necessary to obtain regulatory approval is costly and time consuming. We or our strategic alliance partners may never succeed in achieving marketing approval for any of our product candidates. The probability of success for each product candidate may be affected by numerous factors, including preclinical data, clinical data, competition, manufacturing capability and commercial viability. Under our strategic alliance with GSK, we may be responsible for the development of product candidates through clinical proof-of-concept, depending on the time at which GSK may choose to exercise its option to obtain an exclusive license to develop, manufacture and commercialize product candidates on a program-by-program basis. Under our strategic alliance with Sanofi, we are responsible for the development of product candidates up to initiation of Phase 1 clinical trials, after which time Sanofi would be responsible for the costs of clinical development and commercialization and all related costs. Under our strategic alliance agreement with AstraZeneca, we are responsible for certain research and development activities with respect to each alliance target under a mutually agreed upon research and development plan until the earlier to occur of IND approval in a major market or the end of the research term under the agreement. We also have several independent programs for which we are responsible for all of the research and development costs, unless and until we partner any of these programs in the future.

Most of our product development programs are at an early stage, and successful development of future product candidates from these programs is highly uncertain and may not result in approved products. Completion dates and completion costs can vary significantly for each future product candidate and are difficult to predict. We anticipate we will make determinations as to which programs to pursue and how much funding to direct to each program on an ongoing basis in response to our ability to maintain or enter into new strategic alliances with respect to each program or potential product candidate, the scientific and clinical success of each future product candidate, as well as ongoing assessments as to each future product candidate s commercial potential. We will need to raise additional capital and may seek additional strategic alliances in the future in order to advance our various programs.

General and administrative expenses

General and administrative expenses consist primarily of salaries and related benefits, including stock-based compensation, related to our executive, finance, legal, business development and support functions. Other general and administrative expenses include allocated facility-related costs not otherwise included in research and development expenses, travel expenses and professional fees for auditing, tax and legal services. We expect that general and administrative expenses will increase in the future as we expand our operating activities and incur additional costs associated with being a publicly-traded company. These increases will likely include legal fees, accounting fees, directors and officers liability insurance premiums and fees associated with investor relations.

Other income (expense), net

Other income (expense) consists primarily of interest income and expense, and on occasion income or expense of a non-recurring nature, including changes in debt valuation each reporting period. We earn interest income from interest-bearing accounts and money market funds for cash and cash equivalents and marketable

Table of Contents

securities, such as interest-bearing bonds, for our short-term investments. Interest expense has historically represented the amounts payable to under the convertible notes payable and interest payable under equipment and tenant improvement financing arrangements.

Critical Accounting Policies and Estimates

The preparation of our financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities, disclosure of contingent assets and liabilities, and the revenues and expenses incurred during the reported periods. We base our estimates on historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in the notes to our financial statements appearing elsewhere in this Annual Report, we believe that the following critical accounting policies relating to revenue recognition and stock-based compensation are most important to understanding and evaluating our reported financial results.

Revenue recognition

Our revenues generally consist of upfront payments for licenses or options to obtain licenses in the future, research and development funding and milestone payments under strategic alliance agreements, as well as funding received under government grants. We recognize revenues when all four of the following criteria are met: (1) persuasive evidence that an arrangement exists; (2) delivery of the products and/or services has occurred; (3) the selling price is fixed or determinable; and (4) collectability is reasonably assured.

Strategic Alliance Agreements entered into prior to December 31, 2010

Multiple element arrangements, such as our strategic alliance agreements with GSK, and Sanofi, are analyzed to determine whether the elements within the agreement can be separated or whether they must be accounted for as a single unit of accounting. If the delivered element, which for us is commonly a license or an option to obtain a license in the future, has stand-alone value and the fair value of the undelivered elements, which for us are commonly research and development funding and participation in joint steering committees, can be determined, we recognize revenue separately under the residual method as elements under the arrangement are delivered. If the delivered element does not have stand-alone value or if the fair value of any of the undelivered elements cannot be determined, the arrangement is then accounted for as a single unit of accounting, and we recognize the consideration received under the arrangement as revenue on a straight-line basis over our estimated period of performance, which for us is often the expected term of the research and development plan.

Strategic Alliance Agreements entered into or materially modified after December 31, 2010

In January 2011, we adopted new authoritative guidance on revenue recognition for multiple element arrangements. The guidance, which applies to multiple element agreements entered into or materially modified after December 31, 2010 amends the criteria for separating and allocating consideration in a multiple element agreement by modifying the fair value requirements for revenue recognition and eliminating the use of the residual method. Deliverables under the agreement will be accounted for as separate units of accounting provided that (i) a delivered item has value to the customer on a stand-alone basis; and (ii) if the agreement includes a general right of return relative to the delivered item, delivery or performance of the undelivered item is considered probable and substantially in the control of the vendor. The allocation of consideration amongst the deliverables under the agreement is derived using a best estimate of selling price if vendor specific objective evidence and third-party evidence of fair value is not available. We did not enter into any significant multiple element agreements or materially modify any existing multiple element agreements during 2011. In June 2012,

Table of Contents

we materially modified our strategic alliance agreement with GSK and in July 2012, we materially modified our strategic alliance agreement with Sanofi. In August 2012, we entered into new collaboration and license agreements with both Biogen Idec and AstraZeneca.

Milestones

In January 2011, we adopted new authoritative guidance on revenue recognition for milestone payments related to agreements under which we have continuing performance obligations. We recognize revenue from milestone payments when earned, provided that (i) the milestone event is substantive in that it can only be achieved based in whole or in part on either our performance or on the occurrence of a specific outcome resulting from our performance and its achievability was not reasonably assured at the inception of the agreement, (ii) we do not have ongoing performance obligations related to the achievement of the milestone and (iii) it would result in the receipt of additional payments. A milestone payment is considered substantive if all of the following conditions are met: (i) the milestone payment is non-refundable; (ii) achievement of the milestone was not reasonably assured at the inception of the arrangement; (iii) substantive effort is involved to achieve the milestone; and (iv) the amount of the milestone payments appears reasonable in relation to the effort expended, the other milestones in the arrangement and the related risk associated with the achievement of the milestone. Any amounts received under the agreements in advance of performance, if deemed substantive, are recorded as deferred revenue and recognized as revenue as we complete our performance obligations. The adoption of this guidance did not materially change our previous method for recognizing milestone payments.

Generally, the milestone events contained in our strategic alliance agreements coincide with the progression of our product candidates from target selection, to clinical candidate selection, to clinical trial, to regulatory approval and then to commercialization. The process of successfully discovering a new development candidate, having it approved and ultimately sold for a profit is highly uncertain. As such, the milestone payments we may earn from our partners involve a significant degree of risk to achieve. Therefore, as a product candidate progresses through the stages of its life-cycle, the value of the product candidate generally increases.

Stock-based compensation

We account for stock-based compensation by measuring and recognizing compensation expense for all stock-based payments made to employees and directors based on grant date estimated fair values. We use the accelerated multiple-option approach to allocate compensation cost to reporting periods over each option holder s requisite service period, which is generally the vesting period. Under the accelerated multiple-option approach, also known as the graded-vesting method, we recognize compensation expense over the requisite service period for each separate vesting tranche of the award as though the award was in substance multiple awards, resulting in more expense being recognized in the earlier vesting period of the options.

We estimate the fair value of our stock-based awards to employees and directors using the Black-Scholes model. This estimate is affected by our stock price as well as assumptions, including the risk-free interest rate, expected dividend yield, expected volatility, expected term, expected rate of forfeiture and the fair value of the underlying common stock on the date of grant.

Fair Value Option

Accounting standards for fair value measurements establishes a three-level hierarchy for disclosure of financial instruments measured at fair value. The classification of assets and liabilities within the hierarchy is based on whether the inputs to the measurement valuation methodology are observable or unobservable. Observable inputs reflect market-derived or market-based information obtained from independent sources, while unobservable inputs reflect our estimates about market data. The following three-level fair value hierarchy is based on the transparency of the inputs used to measure the fair value of the financial instruments:

Level 1 includes financial instruments for which quoted market prices for identical instruments are available in active markets.

Table of Contents

Level 2 includes financial instruments for which there are inputs other than quoted prices included in Level 1 that are observable for the asset or liability, either directly or indirectly.

Level 3 includes financial instruments for which fair value is derived from valuation techniques in which one or more significant inputs are unobservable in determining fair values of the instruments.

Applicable accounting policies permit entities to choose, at specified election dates, to measure specified items at fair value if the decision about the election is: 1) applied instrument by instrument, 2) irrevocable, and 3) applied to an entire instrument. In July 2012, we amended and restated the 2010 GSK note, which resulted in a debt extinguishment for accounting purposes. Concurrently with the debt extinguishment, we elected the fair value option for the 2010 GSK note. We used a third party valuation firm to value the 2010 GSK note at the extinguishment date, as of September 30, 2012 and again at December 31, 2012. In future periods, the fair value of the 2010 GSK note will be recorded on a quarterly basis with changes in fair value recorded in non-operating earnings. The 2010 GSK note has been classified in Level 3 within the fair value hierarchy.

The valuation technique applied to the 2010 GSK note uses an income approach in the form of a convertible bond valuation model to value the note. The convertible bond model considers the debt and option characteristics of the note. The key inputs to the model are volatility, risk-free rate and credit spread. The absolute stock and strike price are not key inputs because upon an initial public offering, the conversion option was assumed to be set at-the-money. The estimated fair value of the note was based on the probability weighted average of an initial public offering and a non-initial public offering scenario for the initial valuation in July 2012 and subsequent valuation in September 2012. The December 2012 valuation did not consider a probability weighting, as the initial public offering was completed in October 2012. The volatility inputs are based on historical and implied volatility of peer companies. Peer companies are materially consistent with those used previously in our 409A analyses. The risk-free rate inputs are based on the yield of US Treasury Strips as of each date. The credit spread inputs are based on a creditworthiness analysis of the Company and the guarantors of the 2010 GSK Note, as applicable, and market rates for comparable straight debt instruments.

Our significant accounting policies and estimates are more fully described in Note 1 to the Financial Statements.

Recent Accounting Pronouncements

For a discussion of recently issued accounting pronouncements, refer to the section titled Recently Issued Accounting Pronouncements within The Business, Basis of Presentation and Summary of Significant Accounting Policies of our Financial Statements.

Results of Operations

Comparison of the years ended December 31, 2012 and 2011

The following table summarizes the results of our operations for the years ended December 31, 2012 and 2011, together with the year-over-year changes in those items in dollars (in thousands):

	Years ended December 31,		Change 2012 vs. 2011
	2012	2011	Increase/(Decrease)
Revenue under strategic alliances and grants	$ 12,700	$ 13,789	$ (1,089)
Research and development expenses	20,342	17,289	3,053
General and administrative expenses	4,932	3,637	1,295

Revenue under strategic alliances and grants

We recognized revenue of $12.7 million for the year ended December 31, 2012 compared to $13.8 million for the year ended December 31, 2011. Our revenue during these periods consisted primarily of amortization of

Table of Contents

upfront payments received from the Sanofi and GSK strategic alliances, which we amortize monthly on a straight-line basis over our estimated period of performance. Revenue recognized from the amortization of payments from the Sanofi strategic alliance was $10.0 million for each of the years ended December 31, 2012 and 2011. Revenue recognized from the amortization of payments from the GSK strategic alliance decreased to $2.0 million for the year ended December 31, 2012 from $3.7 million for the year ended December 31, 2011. This reduction was due to the June 2012 amendment of the collaboration agreement which extended our estimated period of performance and the resulting amortization period, applied on a prospective basis. In addition, we entered into a strategic alliance with AstraZeneca, which included an upfront payment of $3.0 million which will be amortized over an estimated performance period of 48 months. This resulted in approximately $0.3 million in revenue for the year ended December 31, 2012.

Concurrently with the collaboration and license agreement, we entered into a Common Stock Purchase Agreement (CSPA) with AstraZeneca, pursuant to which we agreed to sell to AstraZeneca an aggregate of $25.0 million of our common stock in a private placement concurrently with our initial public offering, at a price per share equal to the price at which we sell our common stock to the public in such initial public offering. In October 2012, in accordance with the CSPA, we sold AstraZeneca 6,250,000 shares of our common stock at a price per share of $4.00 (see Note 10). Further, the CSPA stipulated that AstraZeneca could not sell, transfer, make any short sale of, or grant any option for the sale of any common stock for a 365-day period following the effective date of our initial public offering. Accounting guidance for multiple element arrangements contains a presumption that separate contracts negotiated and/or entered into at or near the same time with the same entity were negotiated as a package and should be evaluated as a single agreement. In order to quantify the discount applied to the shares of common stock due to the lack of marketability, we had an independent valuation performed to measure the value of restricting common stock for a period of one year. Based upon restricted stock studies of similar duration and a Black-Scholes valuation to measure the lack of marketability discount, $4.3 million was attributed to the collaboration and license agreement. We will recognize the $4.3 million into revenue ratably over the estimated period of performance of the collaboration.

Research and development expenses

Research and development expenses increased to $20.3 million for the year ended December 31, 2012 compared to $17.3 million for the year ended December 31, 2011. This change was primarily driven by an increase in salaries and related benefits of $1.1 million in response to the incremental research and development personnel required to support the growth in activity within the strategic alliances and collaborations. In conjunction with the increased personnel costs, laboratory supplies and external services costs increased by $1.2 million and $1.6 million, respectively over 2011. These increases were offset by a decrease of approximately $0.8 million in pre-clinical study costs from 2011.

General and administrative expenses

General and administrative expenses increased to $4.9 million for the year ended December 31, 2012 compared to $3.6 million for the year ended December 31, 2011. This change was primarily driven by an increase in salaries and related benefits of $0.9 million, in addition to increases in legal and external service costs of $0.3 million and $0.2 million, respectively, attributable to costs associated with the growth of the business and preparations associated with our initial public offering in October 2012.

Loss on extinguishment of debt

In July 2012, we amended and restated our $5.0 million convertible promissory note originally issued in February 2010 to GSK, or the 2010 GSK note, which resulted in a debt extinguishment for accounting purposes. Concurrently with the debt extinguishment, we elected the fair value option for the 2010 GSK note. We used a third party valuation firm to value the 2010 GSK note at the extinguishment date and again at December 31, 2012. Based on the valuation, we recorded a $1.7 million loss on extinguishment of debt (the difference between

Table of Contents

the original $5.0 million carrying value and the fair value) in the statements of operations and comprehensive loss.

Loss from change in value of convertible note payable

Subsequent to the debt extinguishment previously described, changes in the fair value of the 2010 GSK note has been recorded on a periodic basis with changes in fair value recorded in non-operating earnings. We recorded a loss from valuation of convertible notes payable of $3.0 million in the statements of operations and comprehensive loss for the year ended December 31, 2012.

Comparison of the years ended December 31, 2011 and 2010

The following table summarizes the results of our operations for the years ended December 31, 2011 and 2010, together with the year-over-year changes in those items in dollars (in thousands):

	Year ended December 31,		Change 2011 vs. 2010
	2011	2010	Increase/(Decrease)
Revenue	$ 13,789	$ 8,601	$ 5,188
Research and development expenses	17,289	20,178	(2,889)
General and administrative expenses	3,637	3,921	(284)

Revenue under strategic alliances and grants

We recognized revenue of $13.8 million for the year ended December 31, 2011 compared to $8.6 million for the year ended December 31, 2010. Our revenue during these periods consisted primarily of amortization of upfront payments received from the Sanofi and GSK strategic alliances, which we amortize monthly on a straight-line basis over our estimated period of performance. Revenue recognized from the amortization of payments from the Sanofi strategic alliance was $10.0 million and $5.0 million for the years ended December 31, 2011 and 2010, respectively. Total revenue recognized from upfront payments received from GSK was $3.2 million and $3.1 million for the years ended December 31, 2011 and 2010, respectively. We amortize our upfront payments monthly on a straight-line basis over the period of performance. As a result, in 2010, we amortized six months and ten months of upfront payments from Sanofi and GSK, respectively. In July 2011, we earned a $500,000 milestone payment under our strategic alliance agreement with GSK. In November 2010, we were awarded $489,000 from the United States Department of Treasury for two projects qualifying under the Qualifying Therapeutic Discovery Project Program to support research with the potential to produce new therapies. These awards represent a one-time payment to us, and we do not anticipate any additional funding in the future under the Qualifying Therapeutic Discovery Project Program.

Research and development expenses

Research and development expenses decreased to $17.3 million for the year ended December 31, 2011 compared to $20.2 million for the year ended December 31, 2010. The decrease of approximately $2.9 million is primarily related to a $3.8 million reduction in sublicense fees paid to Alnylam and Isis in 2010 for our Sanofi strategic alliance and a $0.3 million reduction in external services, offset by an increase of $1.1 million in payroll and related benefits related to an increase in research and development personnel.

General and administrative expenses

General and administrative expenses decreased to $3.6 million for the year ended December 31, 2011 compared to $3.9 million for the year ended December 31, 2010. The decrease of approximately $0.3 million is primarily related to a $0.3 million reduction in annual performance bonuses, a $0.3 million reduction in support

Table of Contents

services received from Isis and a $0.2 million reduction in expenses incurred to secure our strategic alliance with Sanofi, offset by an increase in payroll and related benefits of $0.5 million.

Liquidity and Capital Resources

Since our inception through December 31, 2012, we have raised $190.4 million to fund our operations primarily through upfront payments, research funding and preclinical milestones from our strategic alliances, from government grants and from the sale of our equity and convertible debt securities. Through December 31, 2012, we have received $65.4 million principally from upfront payments, research funding and preclinical milestones from our strategic alliances with GSK and Sanofi and government grants, and $125.0 million from the sale of our equity and convertible debt securities, including $70.0 million in net proceeds from our initial public offering and concurrent private placement of our common stock in October 2012.

As of December 31, 2012, we had approximately $98.1 million in cash and cash equivalents and short-term investments. The following table shows a summary of our cash flows for the years ended December 31, 2012, 2011 and 2010:

	Year ended December 31,		
	2012	**2011**	**2010**
Net cash provided by (used in):			
Operating activities	$ (8,721)	$ (15,063)	$ 12,307
Investing activities	(30,384)	3,324	(21,960)
Financing activities	70,482	(354)	14,693

Operating activities

Net cash used in operating activities decreased to $8.7 million for the year ended December 31, 2012, compared to net cash used in operating activities of $15.1 million for the year ended December 31, 2011. The impact of the increase in net loss of $17.4 million for the year ended December 31, 2012 compared to $7.6 million for the year ended December 31, 2011 was offset in part by the non-cash add-back of approximately $4.7 million in charges associated with the loss on extinguishment of debt and subsequent change in value of the 2010 GSK Note. Proceeds from upfront payments associated with strategic alliances and collaboration agreements increased to $13.0 million for the year ended December 31, 2012, compared to $5.5 million for the year ended December 31, 2011. In 2012, this included $4.3 million in proceeds from the CSPA that was attributed to the collaboration and license agreement with AstraZeneca. As a result, changes in deferred revenue resulted in a net cash inflow of $0.5 million for the year ended December 31, 2012 compared to a net cash outflow of $8.2 million for the year ended December 31, 2011.

Net cash used in operating activities was $15.1 million for the year ended December 31, 2011, compared to net cash provided by operating activities of $12.3 million for the year ended December 31, 2010. The change between years was primarily driven by the receipt of $33.0 million in upfront payments from our strategic alliances with GSK and Sanofi in 2010.

Investing activities

Net cash used in or provided by investing activities for the periods presented primarily relate to the purchase, sale and maturity of investments used to fund the day-to-day needs of our business. In the years ended December 31, 2012 and 2010 cash provided by financing activities provided a surplus of cash which was then used to purchase short-term investments. The net investment of short-term investments was $29.0 million and $19.5 million in the years ended December 31, 2012 and 2010, respectively. Investing activities included the net sales and maturities of short-term investments of $3.9 million for the year ended December 31, 2011.

Financing activities

Net cash provided by financing activities was approximately $70.5 million for the year ended December 31, 2012, compared to $0.4 million net cash used in financing activities for the same period in 2011. This increase is

Table of Contents

a result of net proceeds from our initial public offering and concurrent private placement of our common stock of approximately $65.8 million in October 2012, which excludes $4.3 million in proceeds from the private placement attributed to the collaboration and license agreement with AstraZeneca, in addition to proceeds of $5.0 million from the issuance of a promissory note to Biogen Idec in conjunction with our license and collaboration agreement in August 2012.

Net cash used in financing activities was $0.4 million for the year ended December 31, 2011 compared to cash provided by financing activities of $14.7 million for the year ended December 31, 2010. In 2010, we raised a total of $15.0 million through the issuance of a $5.0 million convertible note to GSK and the issuance of $10.0 million of series B convertible preferred stock to Sanofi.

Future Financing Requirements

We believe that our existing cash and cash equivalents and short-term investments as of December 31, 2012 will be sufficient to meet our anticipated cash requirements into 2016. However, our forecast of the period of time through which our financial resources will be adequate to support our operations is a forward-looking statement that involves risks and uncertainties, and actual results could vary materially.

Our future capital requirements are difficult to forecast and will depend on many factors, including:

- the achievement of milestones under our strategic alliance agreements with GSK, Sanofi and AstraZeneca;
- the terms and timing of any other strategic alliance, licensing and other arrangements that we may establish;
- the initiation, progress, timing and completion of preclinical studies and clinical trials for our potential product candidates;
- the number and characteristics of product candidates that we pursue;
- the progress, costs and results of our clinical trials;
- the outcome, timing and cost of regulatory approvals;
- delays that may be caused by changing regulatory requirements;
- the cost and timing of hiring new employees to support our continued growth;
- the costs involved in filing and prosecuting patent applications and enforcing and defending patent claims;
- the costs and timing of procuring clinical and commercial supplies of our product candidates;
- the costs and timing of establishing sales, marketing and distribution capabilities; and

the extent to which we acquire or invest in businesses, products or technologies.

Contractual Obligations and Commitments

The following is a summary of our long-term contractual obligations as of December 31, 2012 (in thousands):

		Payments due by period			
	Total	2013 <1 year	2014-2015 2-3 Years	2016-2017 4-5 Years	>5 Years
Operating lease obligation relating to facility[1]	$ 4,523	$ 732	$ 2,062	$ 1,729	
Principal under convertible notes payable, excluding accrued interest[2]	5,427		5,427		
Total	$ 9,950	$ 732	$ 7,489	$ 1,729	

Table of Contents

(1) We lease 21,834 square feet for office and laboratory space in La Jolla, California under an operating lease that expires in June 2017. In November 2012, we amended our lease to expand our laboratory and office space by approximately 7,000 square feet, effective May 2013. Obligations under all lease agreements are included in the above table.

(2) In October 2012, in conjunction with our initial public offering we issued GSK a convertible promissory note, or the Post-IPO GSK Note, in the principal amount of $5.4 million. The Post-IPO GSK Note has a maturity date of October 9, 2015. At GSK s option, the Post-IPO GSK Note may be converted into shares of our common stock s 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, regardless of the then fair market value of our common stock.

License Agreements

Prior to 2011, our access to the Tuschl 3 patents was derived from agreements between Max-Planck-Innovation GmbH, or Max-Planck, and our founding companies, Alnylam and Isis, for exclusive use in *micro*RNA therapeutics. In April 2011, we entered into a direct, co-exclusive license with Max-Planck. The license provides to us, Alnylam and Isis, co-exclusively, access to the Tuschl 3 patents for therapeutic use. We will be required to make payments based upon the initiation of clinical trials and/or product approval milestones totaling up to $1.6 million for each licensed product reaching such clinical stage. In addition to milestone payments, we will be required to pay royalties of a percentage of cumulative annual net sales of a licensed product commercialized by us or one of our strategic alliance partners. The percentage is in the low single digits, with the exact percentage depending upon whether the licensed product incorporates intellectual property covered by a Tuschl 3 patent that is still subject to a pending application or, alternatively an issued patent, and also upon the volume of annual sales. Reduction in the royalties paid to Max-Planck is made for any third party payments also required to be made with a minimum floor in the low single digits.

In June 2009, we entered into a co-exclusive license for use of the Tuschl 3 patents for diagnostic purposes with Max-Planck. Under the terms of the license, we made an aggregate initial payment to Max-Planck of 175,000 in three installments together with interest, with 75,000 paid in June 2009 and 50,000 plus interest paid in each of June 2010 and December 2010. In addition, we made annual maintenance payments of 10,000 in 2011 and 20,000 in 2012 and will make an increased annual maintenance payment commencing in 2013 and thereafter during the term of the agreement. In addition to maintenance payments, we will be required to pay royalties of a percentage of net sales of licensed products. The percentage is in the mid-single digits in the event we market the product and low double digits in the event we sell the product through a distributor. The royalties payable to Max-Planck are reduced by the royalties payable to third parties but only if aggregate royalties payable to Max-Planck and third parties exceed a percentage in the mid-10 to 20% range.

In May 2010, we exclusively licensed patent rights from Julius-Maximilians-Universität Würzburg and Bayerische Patent Allianz GmBH, which we collectively refer to herein as the University of Würzburg, which rights encompass the use of anti-miR therapeutics targeting miR-21 for the treatment of fibrosis, including kidney, liver, lung and cardiac fibrosis. As a license issuance fee, we paid the University of Würzburg 300,000. In addition, upon commercialization of a product, we will pay to the University of Würzburg a percentage of net sales as a royalty. This royalty is in the low single digits and is reduced upon expiration of all patent claims covering the product. We also paid the University of Würzburg a partnership bonus of 200,000 upon entering into our strategic alliance agreement with Sanofi. Under the agreement, beginning January 1, 2020 and ending on the date we receive NDA approval for a licensed product, we will accrue a minimum royalty obligation of 150,000 per year, which will become payable upon approval of an NDA for a licensed product. After approval of an NDA for a licensed product, we will pay the University of Würzburg an annual minimum royalty, which increases in the five years following approval up to a maximum of 3.0 million per year. The minimum royalties are creditable against actual royalties due and payable for the same calendar year.

Table of Contents

In August 2005, Alnylam and Isis entered into a co-exclusive license agreement with Stanford University, or Stanford, relating to its patent applications claiming the use of miR-122 to reduce the replication of HCV. Upon our formation, we received access to the Stanford technology as an affiliate of Alnylam and Isis. In July 2009, Isis assigned its rights and obligations under the license agreement to us. We are permitted to sublicense our rights under the agreement in connection with a bona fide partnership seeking to research and/or develop products under a jointly prepared research plan and which also includes a license to our intellectual property or in association with providing services to a sublicensee. In the event we receive an upfront payment in connection with a sublicense, we are obligated to pay to Stanford a one-time payment, the amount of which will vary depending upon the size of upfront payment we receive. We must also make an annual license maintenance payment during the term of the agreement. The maintenance payments are creditable against royalty payments made in the same year. We will be required to pay milestones for an exclusively licensed product which will be payable upon achievement of specified regulatory and clinical milestones in an aggregate amount of up to $400,000. Milestones for a non-exclusively licensed product will be payable upon achievement of the same milestones in an aggregate amount of up to $200,000. Upon commercialization of a product, we will be required to pay to Stanford a percentage of net sales as a royalty. This percentage is in the low single digits. The payment will be reduced by other payments we are required to make to third parties until a minimum royalty has been reached.

In March 2011, we entered into an exclusive license with NYU related to our miR-33 program. Under the terms of the agreement, we paid to NYU an upfront payment of $25,000. An equal additional payment will be required upon issuance of a patent containing a claim of treating or preventing disease. We will be required to make payments to NYU upon achievement of specified clinical and regulatory milestones of up to an aggregate of $925,000. These milestone payments will only be made after issuance of a therapeutic claim under the NYU patent applications. We are also required to pay royalties of a percentage of net sales for any product sold by us or a strategic alliance partner. The royalty rate is in the low single digits and is reduced down to a minimum floor in the event we are required to pay royalties to a third party. In the event we sublicense the NYU patents, NYU is also entitled to receive a percentage of the sublicense income received by us. The percentage payable depends upon the development stage of the program when the sublicense is completed with the highest percentage paid with submission of the first IND. The percentage thereafter declines until completion of the first Phase 2 clinical trial.

We enter into contracts in the normal course of business with contract research organizations for preclinical research studies, research supplies and other services and products for operating purposes. These contracts generally provide for termination on notice, and therefore are cancelable contracts and not included in the table of contractual obligations and commitments.

Off-Balance Sheet Arrangements

We do not have any off-balance sheet arrangements (as defined by applicable SEC regulations) that are reasonably likely to have a current or future material effect on our financial condition, results of operations, liquidity, capital expenditures or capital resources.

JOBS Act

In April 2012, the JOBS Act was enacted. Section 107 of the JOBS Act provides that an emerging growth company can take advantage of the extended transition period provided in Section 7(a)(2)(B) of the Securities Act for complying with new or revised accounting standards. Thus, an emerging growth company can delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this extended transition period and, as a result, we will adopt new or revised accounting standards on the relevant dates on which adoption of such standards is required for other companies.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

Some of the securities that we invest in have market risk in that a change in prevailing interest rates may cause the principal amount of the marketable securities to fluctuate. Financial instruments that potentially subject

Table of Contents

us to significant concentrations of credit risk consist primarily of cash, cash equivalents and short-term investments. We invest our excess cash primarily in commercial paper and debt instruments of financial institutions, corporations, U.S. government-sponsored agencies and the U.S. Treasury. The primary objectives of our investment activities are to ensure liquidity and to preserve principal while at the same time maximizing the income we receive from our marketable securities without significantly increasing risk. Additionally, we established guidelines regarding approved investments and maturities of investments, which are designed to maintain safety and liquidity.

Because of the short-term maturities of our cash equivalents and marketable securities, we do not believe that an increase in market rates would have any significant impact on the realized value of our marketable securities. If a 10% change in interest rates were to have occurred on December 31, 2012, this change would not have had a material effect on the fair value of our investment portfolio as of that date.

Item 8. Financial Statements and Supplementary Data

Table of Contents

Report of Independent Registered Public Accounting Firm

The Board of Directors and Stockholders of Regulus Therapeutics Inc.

We have audited the accompanying balance sheets of Regulus Therapeutics Inc. as of December 31, 2012 and 2011, and the related statements of operations and comprehensive loss, convertible preferred stock and stockholders equity (deficit), and cash flows for each of the three years in the period ended December 31, 2012. These financial statements are the responsibility of the Company s management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. We were not engaged to perform an audit of the Company s internal control over financial reporting. Our audits included consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Company s internal control over financial reporting. Accordingly we express no such opinion. An audit also includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the financial position of Regulus Therapeutics Inc. at December 31, 2012 and 2011, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2012, in conformity with U.S. generally accepted accounting principles.

/s/ Ernst & Young LLP

San Diego, California

February 19, 2013

Table of Contents

Regulus Therapeutics Inc.

BALANCE SHEETS

(in thousands, except share and per share data)

	December 31, 2012	December 31, 2011
Assets		
Current assets:		
Cash and cash equivalents	$ 40,552	$ 9,175
Short-term investments	57,548	28,969
Prepaid and other current assets	829	522
Total current assets	98,929	38,666
Property and equipment, net	3,310	3,110
Intangible assets, net	1,154	980
Other assets	125	125
Total assets	$ 103,518	$ 42,881
Liabilities and stockholders equity (deficit)		
Current liabilities:		
Accounts payable	$ 311	$ 501
Accrued liabilities	658	943
Accrued compensation	1,348	671
Current portion of deferred revenue	10,451	10,735
Total current liabilities	12,768	12,850
Convertible notes payable, at fair value	10,134	
Convertible note payable		10,000
Deferred revenue, less current portion	17,756	16,987
Other long-term liabilities	767	1,847
Total liabilities	41,425	41,684
Series A convertible preferred stock, $0.001 par value; no shares and 25,000,000 shares authorized at December 31, 2012 and 2011, respectively; no shares and 24,900,000 shares issued and outstanding at December 31, 2012 and 2011, respectively; liquidation preference of $$0 and 49,800 at December 31, 2012 and 2011, respectively		32,691
Series B convertible preferred stock, $0.001 par value; no shares and 2,500,000 shares authorized at December 31, 2012 and 2011, respectively; no shares and 2,499,999 shares issued and outstanding at December 31, 2012 and 2011, respectively; liquidation preference of $0 and $10,000 at December 31, 2012 and 2011, respectively		10,000
Stockholders equity (deficit):		
Common stock, $0.001 par value; 200,000,000 and 38,600,000 shares authorized at December 31, 2012 and 2011, respectively, 35,831,808 and 153,184 shares issued and outstanding at December 31, 2012 and 2011,respectively	36	
Additional paid-in capital	122,528	1,584
Accumulated other comprehensive loss	(52)	(67)
Accumulated deficit	(60,419)	(43,011)
Total stockholders equity (deficit)	62,093	(41,494)

Total liabilities and stockholders equity	$ 103,518	$ 42,881

See accompanying notes to these financial statements.

Table of Contents

Regulus Therapeutics Inc.

STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS

(in thousands, except share and per share data)

	Year ended December 31,		
	2012	**2011**	**2010**
Revenues:			
Revenue under strategic alliances and collaborations	$ 12,700	$ 13,767	$ 8,112
Grant revenue		22	489
Total revenues	12,700	13,789	8,601
Operating expenses:			
Research and development	20,342	17,289	20,178
General and administrative	4,932	3,637	3,921
Total operating expenses	25,274	20,926	24,099
Loss from operations	(12,574)	(7,137)	(15,498)
Other income (expense):			
Interest and other income	110	129	271
Interest expense	(247)	(388)	(362)
Loss on extinguishment of debt	(1,738)		
Loss from change in value of convertible note payable	(2,969)		
Loss before income taxes	(17,418)	(7,396)	(15,589)
Income tax (benefit) expense	(10)	206	(30)
Net loss	$ (17,408)	$ (7,602)	$ (15,559)
Other comprehensive loss:			
Unrealized gain (loss) on short-term investments, net	15	(80)	13
Comprehensive loss	$ (17,393)	$ (7,682)	$ (15,546)
Net loss per share, basic and diluted	$ (2.12)	$ (85.82)	
Shares used to compute basic and diluted net loss per share	8,212,538	88,582	

See accompanying notes to these financial statements.

Table of Contents

Regulus Therapeutics Inc.

STATEMENTS OF CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS EQUITY (DEFICIT)

(in thousands, except share data)

	Series A convertible preferred stock		Series B convertible preferred stock		Common stock		Additional paid-in capital	Accumulated other comprehensive income (loss)	Accumulated deficit	Total stockholders equity (deficit)
	Shares	Amount	Shares	Amount	Shares	Amount				
Balance at December 31, 2009	24,900,000	$ 32,691		$		$	$ 98	$	$ (19,850)	$ (19,752)
Issuance of series B convertible preferred stock			2,499,999	10,000						
Stock-based compensation expense							603			603
Unrealized gain on short-term investments								13		13
Net loss									(15,559)	(15,559)
Balance at December 31, 2010	24,900,000	32,691	2,499,999	10,000			701	13	(35,409)	(34,695)
Issuance of common stock upon exercise of options					153,184		58			58
Stock-based compensation expense							825			825
Unrealized loss on short-term investments								(80)		(80)
Net loss									(7,602)	(7,602)
Balance at December 31, 2011	24,900,000	32,691	2,499,999	10,000	153,184		1,584	(67)	(43,011)	(41,494)
Issuance of common stock upon exercise of options					294,374		138			138
Stock-based compensation expense							1,550			1,550
Impact of initial public offering on stockholders equity (deficit):										
Effect of 2-for-1 split on shares of preferred stock	(12,450,000)		(1,250,000)							
Conversion of shares of preferred stock to common stock	(12,450,000)	(32,691)	(1,249,999)	(10,000)	13,699,999	14	42,677			42,691
Initial public offering of common stock, net of $5,886 of offering costs					12,730,982	13	45,025			45,038
Issuance of common stock in private placement concurrently with initial public offering, net					6,250,000	6	20,744			20,750
Conversion of notes payable to common stock					2,703,269	3	10,810			10,813
Unrealized loss on short-term investments, net of tax								15		15
Net loss									(17,408)	(17,408)
Balance at December 31, 2012		$		$	35,831,808	$ 36	$ 122,528	$ (52)	$ (60,419)	$ 62,093

See accompanying notes to these financial statements.

Table of Contents

Regulus Therapeutics Inc.

STATEMENTS OF CASH FLOWS

(in thousands)

	Year ended December 31,		
	2012	2011	2010
Operating activities			
Net loss	$ (17,408)	$ (7,602)	$ (15,559)
Adjustments to reconcile net loss to net cash provided by (used in) operating activities:			
Depreciation and amortization expense	1,017	911	494
Loss from change in value of convertible note payable	2,969		
Loss on extinguishment of debt	1,738		
Amortization of premium on investments, net	422	551	522
Gain on investments	(28)	(1)	(4)
Stock-based compensation	1,550	825	603
Loss on disposal of long-term assets	36		
Deferred income taxes			394
Change in operating assets and liabilities:			
Prepaid and other current assets	(308)	(136)	(351)
Accounts payable	(189)	(1,345)	574
Accrued compensation	677	(528)	500
Accrued liabilities	(20)	29	(311)
Deferred revenue	486	(8,219)	24,888
Deferred rent and other liabilities	337	452	557
Net cash (used in) provided by operating activities	(8,721)	(15,063)	12,307