

Regulus Therapeutics Inc.  
Form 10-K  
February 23, 2016  
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UNITED STATES  
SECURITIES AND EXCHANGE COMMISSION  
WASHINGTON, D.C. 20549

FORM 10-K

(Mark One)

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

FOR THE FISCAL YEAR ENDED DECEMBER 31, 2015

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 (I.R.S. Employer  
Incorporation or Organization) Identification No.)

3545 John Hopkins Ct., Suite 210 92121  
San Diego, CA  
(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 Global Market  
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

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

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  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  No

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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

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

As of June 30, 2015, the last business day of the registrant's most recently completed second fiscal quarter, the aggregate market value of the registrant's common stock held by non-affiliates of the registrant was approximately \$577.7 million, based on the closing price of the registrant's common stock on the NASDAQ Global Market on June 30, 2015 of \$10.96 per share.

The number of outstanding shares of the registrant's common stock, par value \$0.001 per share, as of February 19, 2016 was 52,704,783.

**DOCUMENTS INCORPORATED BY REFERENCE**

Portions of the registrant's proxy statement to be filed with the Securities and Exchange Commission pursuant on Schedule 14A in connection with the registrant's 2016 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, 2015.

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Signatures

The Regulus Therapeutics logo is a trademark of Regulus Therapeutics Inc. We use “Regulus Therapeutics” as a trademark in the United States and other countries. We have registered this trademark in the United States, the European Union and Switzerland. We use “microMarkers” as a servicemark in the United States and other countries. We have filed for registration of this servicemark in the United States. All other product and company names are trademarks of their respective companies.

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PART I

Forward-Looking Statements

This Annual Report on Form 10-K 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 words indicating future results, though not all forward-looking statements necessarily contain these identifying words. Such statements may include, but are not limited to, statements concerning the following:

- the initiation, cost, timing, progress and results of, and our expected ability to undertake certain activities and accomplish certain goals with respect to, our research and development activities, preclinical studies and clinical trials;
- our ability to obtain and maintain regulatory approval of our product candidates, and any related restrictions, limitations, and/or warnings in the label of an approved product candidate;
- our ability to obtain funding for our operations;
  - our plans to research, develop and commercialize our product candidates;
- our strategic alliance partners’ election to pursue development and commercialization;
- our ability to attract collaborators with development, regulatory and commercialization expertise;
- future activities to be undertaken by our strategic alliance partners, collaborators and other third parties;
- our ability to obtain and maintain intellectual property protection for our product candidates;
- the size and growth potential of the markets for our product candidates, and our ability to serve those markets;
- our ability to successfully commercialize, and our expectations regarding future therapeutic and commercial potential with respect to, our product candidates;
- the rate and degree of market acceptance of our product candidates;
- our ability to develop sales and marketing capabilities, whether alone or with potential future collaborators;
- regulatory developments in the United States and foreign countries;
- the performance of our third-party suppliers and manufacturers;
- the success of competing therapies that are or may become available;
- the loss of key scientific or management personnel;
- our ability to successfully secure and deploy capital;
- our ability to satisfy our debt obligations;
- our expectations regarding the time during which we will be an emerging growth company under the Jumpstart Our Business Startups Act of 2012, or the JOBS Act;
- our use of the proceeds from our prior public offerings;
- the accuracy of our estimates regarding expenses, future revenues, capital requirements and need for additional financing; and
- the risks and other forward-looking statements described under the caption “Risk Factors” under Part I, Item 1A of this Annual Report on Form 10-K.

Item 1. Business

OVERVIEW

We are a biopharmaceutical company focused on discovering and developing first-in-class drugs that target microRNAs to treat a broad range of diseases. We were formed in 2007 when Alnylam Pharmaceuticals, Inc.

and Ionis Pharmaceuticals, Inc.(formerly Isis Pharmaceuticals, Inc.) contributed significant intellectual property, know-how and financial and human capital to pursue the development of drugs targeting microRNAs pursuant to a license and collaboration agreement. We have established strategic alliances with AstraZeneca AB and Sanofi to discover, develop and commercialize microRNA therapeutics.

microRNAs are naturally occurring ribonucleic acid, or RNA, molecules that play a critical role in regulating key biological pathways. Scientific research has shown that the improper balance, or dysregulation, of microRNAs is directly linked to many diseases. To date, approximately 500 microRNAs have been identified in humans, each of which is believed to interact with a specific set of genes that control key aspects of cell biology. Since most diseases are multi-factorial and involve multiple

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targets in a pathway, the ability to modulate gene networks by targeting a single microRNA provides a new therapeutic approach for treating complex diseases.

RNA plays an essential role in the process used by cells to encode and translate genetic information from DNA to proteins. RNA is comprised of subunits called nucleotides and is synthesized from a DNA template by a process known as transcription. Transcription generates different types of RNA, including messenger RNAs that carry the information for proteins in the sequence of their nucleotides. In contrast, microRNAs are RNAs that do not code for proteins but rather are responsible for regulating gene expression by affecting the translation of target messenger RNAs. By interacting with many messenger RNAs, a single microRNA can regulate several genes that are instrumental for the normal function of a biological pathway.

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

- microRNAs, until recently, have not been a focus of pharmaceutical research;
- microRNAs play a critical role in regulating biological pathways by controlling the translation of many target genes;
- microRNA therapeutics target entire disease pathways which may result in more effective treatment of complex multi-factorial diseases; and

- microRNA therapeutics may be synergistic with other therapies because of their different mechanism of action.

We believe we have assembled the leading position in the microRNA field, including expertise in microRNA biology and oligonucleotide chemistry, a broad intellectual property estate, relationships with key opinion leaders and a disciplined drug discovery and development process. We refer to these assets as our microRNA product platform. We are using our microRNA product platform to develop chemically modified, single-stranded oligonucleotides that we call anti-miRs to modulate microRNAs and return diseased cells to their healthy state. We believe microRNAs may be transformative in the field of drug discovery and that anti-miRs may become a new and major class of drugs with broad therapeutic application, much like small molecules, biologics and monoclonal antibodies. In addition to our microRNA product platform, we have established Regulus microMarkers<sup>SM</sup>, a division focused on identifying microRNAs as biomarkers of human disease to support our therapeutic pipeline, collaborators and strategic partners. Regulus microMarkers<sup>SM</sup> utilizes a clinically-validated, highly reproducible technology platform to identify microRNAs as potential biomarkers for disease and we control key intellectual property and know-how related to the division. We believe that microRNA biomarkers may be used to select optimal patient segments in clinical trials and to monitor disease progression or relapse. We believe these microRNA biomarkers can be applied toward drugs that we develop and drugs developed by other companies with which we partner or collaborate. We have completed a research collaboration with Biogen focused on the discovery of microRNAs as biomarkers for multiple sclerosis and have also completed research for another leading, commercial-stage pharmaceutical company to explore microRNAs as biomarkers for specific patient populations. We also maintain several academic research collaborations focused on the identification of microRNAs as biomarkers in multiple disease areas.

### ‘Clinical Map Initiative’ Goals

To advance our microRNA therapeutics pipeline and biomarkers platform over the next several years, we have outlined specific goals under our ‘Clinical Map Initiative’ strategy. We are developing RG-101, a GalNAc-conjugated anti-miR targeting miR-122, a host factor for the hepatitis C virus, or HCV, infection. In addition, we are developing RG-012, an anti-miR targeting microRNA-21 for the treatment of Alport syndrome, a life-threatening kidney disease driven by genetic mutations with no approved therapy. We are also advancing several programs toward clinical development in areas such as oncology and fibrosis, both independently and with our strategic alliance partners AstraZeneca and Sanofi. Under our strategic alliance with AstraZeneca, AstraZeneca recently commenced clinical development of RG-125, a GalNAc-conjugated anti-miR targeting microRNA-103/107 for the treatment of nonalcoholic steatohepatitis, or NASH, in patients with type 2 diabetes/pre-diabetes.

RG-101: In August 2015, we initiated a Phase II study investigating RG-101 designed to evaluate a shortened, four-week treatment regimen containing a subcutaneous administration of 2 mg/kg of RG-101 at Day 1 and Day 29, in combination with oral direct-acting antiviral agents Harvoni®, Olysio®, and Daklinza® for 28 days. In February, 2016, we announced interim results from the clinical study. Thirty-eight patients had been evaluated through 8 weeks

of follow up. Ninety-seven percent of those patients (37/38) had HCV RNA viral load measurements below the limit of quantification. For those patients through 12 weeks of follow-up, 100% remained below the limit of quantification (14/14). To date, RG-101 has been generally well tolerated with the majority of adverse events considered mild or moderate (headache and fatigue most commonly reported, each at approximately 11%), two SAEs reported during the follow-up period, and with no study discontinuations. The primary endpoint analysis (12 week follow up) for all 79 patients in the study are anticipated to be reported in second quarter of 2016. To expand the potential development of RG-101, in November 2015 we entered into a clinical trial collaboration and



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formulation agreement with GSK LLC. In the first quarter of 2016, we plan to initiate a Phase II study evaluating the potential to achieve sustained viral responses post treatment with a single subcutaneous administration of RG-101 in combination with daily oral administrations of GSK2878175, a non-nucleoside NS5B polymerase inhibitor, for up to 12 weeks in treatment-naïve patients chronically infected with HCV genotypes 1 and 3. Concurrently, GSK will work on developing a long-acting parenteral formulation for injection (“LAP”) of GSK2878175 which could improve patient compliance through reduced dosing intervals and potentially extend opportunities for HCV therapeutic intervention. This LAP formulation of GSK2878175 may be used in potential additional clinical trials together with RG-101 following completion of the planned Phase II study. Neither we nor GSK has any further obligations or commitments beyond the contemplated study under the clinical trial collaboration agreement.

RG-012: In June 2015, we initiated a Phase I study to evaluate the safety, tolerability and pharmacokinetics of subcutaneous dosing of RG-012 in healthy volunteers and the study is now complete. Forty healthy volunteer subjects were enrolled in this first-in-human, single ascending dose study. RG-012 was well-tolerated and there were no serious adverse events reported. We also continue to enroll Alport syndrome patients in our global ATHENA natural history of disease study, which is designed to characterize the natural decline of renal function (as measured by established renal markers) in Alport syndrome patients over time. We believe the data from the ATHENA study will provide the clinical basis for the design of a Phase II proof-of-concept study to monitor the therapeutic effect of RG-012 on the decline in renal function in patients with Alport syndrome. We plan to initiate a Phase II proof-of-concept study evaluating the efficacy of RG-012 in Alport syndrome patients during 2016.

RG-125: AstraZeneca initiated a Phase I study evaluating RG-125 in humans in December 2015, earning Regulus a \$10.0 million milestone from the collaboration. AstraZeneca is responsible for all future development for RG-125. Our microRNA product platform

We are the leading company in the field of microRNA therapeutics and are uniquely positioned to leverage oligonucleotide technologies that have been proven in clinical trials by us and our founding companies, Alnylam and Ionis Pharmaceuticals, Inc. (formerly Isis Pharmaceuticals, Inc.). Central to achieving our goals is the know-how that we have accumulated in oligonucleotide design and how the specific chemistries behave in the clinical setting.

We view the following as providing a competitive advantage for our microRNA product platform:

- a mature platform selectively producing multiple development candidates advancing to the clinic;
- scientific advisors who are pioneers in the microRNA field;
- exclusive access to proven RNA therapeutic technologies through our founding companies, such as GalNac conjugation and the corresponding manufacturing rights licensed to us from Alnylam, which we are utilizing to enhance delivery of RG-101, our wholly-owned GalNac-conjugated anti-miR targeting microRNA-122, to hepatocytes to more effectively treat HCV.
- a leading microRNA intellectual property estate with access to approximately 850 patents and patent applications relating to RNA technologies, including patent and patent applications relating to chemical modification of oligonucleotides that are useful for microRNA therapeutics, and over 200 patents and patent applications covering compositions and therapeutic uses related to microRNA and microRNA drug products;
- development expertise and financial resources provided by our strategic alliances; and
- numerous academic collaborations that help us identify new microRNA targets and support our early stage discovery efforts.

The disciplined approach we take for the discovery and development of microRNA 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 microRNA 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 microRNA in a disease;
- availability of predictive preclinical disease models to test our microRNA 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



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We identify microRNA targets through bioinformatic analysis of public and proprietary microRNA expression profiling data sets from samples of diseased human tissues. The analysis of such data sets can immediately highlight a potential role for specific microRNAs in the disease being studied. Further investigation of animal models that are predictive of human diseases in which those same microRNAs 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 microRNA 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 microRNA in healthy animals can create the specific disease state and inhibition of the microRNA can lead to a therapeutic benefit. Second, using animal models predictive of human diseases, we determine whether pharmacological modulation of the up-regulated microRNA target with our anti-miRs can also lead to a therapeutic benefit. This validation process enables us to prioritize microRNA targets that appear to be key drivers of disease and not simply correlating markers.

### Step 4 - Optimization of microRNA development candidates

We have developed a proprietary process that allows us to rapidly generate an optimized development candidate. Unlike traditional drug classes, such as small molecules, in which thousands of compounds must be screened to identify prospective leads, the fact that anti-miRs are mirror images of their target microRNAs 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 microRNA target is causing disease.

### Regulus microMarkers<sup>SM</sup>

In January 2014, we established Regulus microMarkers<sup>SM</sup>, a division focused on identifying microRNAs as biomarkers of human disease, which is designed to support our therapeutic pipeline, collaborators and strategic partners. Through our microRNA target identification and validation efforts we have developed proprietary technologies for microRNA profiling and analysis of human clinical samples such as tissue. More recently, microRNAs have been detected in bodily fluids such as blood, and emerging data generated by us and others have demonstrated that microRNA signatures in blood can mimic the expression profile observed in disease tissues. The identification of dysregulated microRNAs from various human tissues and blood helps us identify and validate potential microRNA targets for therapeutic development. Equally important, such microRNAs may become biomarkers that can be used to select optimal patient segments for our clinical trials and the clinical trials of our strategic alliance partners and collaborators.

### Our initial development candidates

We are developing single-stranded oligonucleotides, which are chemically synthesized chains of nucleotides that are mirror images of specific target microRNAs. 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 microRNA target that is up-regulated in a cell and that is involved in the disease state. In binding to the microRNA, anti-miRs correct the dysregulation and return diseased cells to their healthy state. We have demonstrated the therapeutic benefit of inhibiting microRNA-122 in humans with RG-101 in HCV patients. In addition to these human proof-of-concept results, we have demonstrated therapeutic benefits of our anti-miRs in over 20 different preclinical models of human diseases.

We have identified and validated several microRNA targets across a number of disease categories and are working independently and with our strategic alliance partners to optimize anti-miR development candidates. We intend 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 oncology 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 may seek to secure partners with requisite expertise and resources.



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\*Sanofi will have the exclusive option, exercisable after proof-of-concept, to take over further development and commercialization of these programs. At this stage, Regulus will have the option to co-promote any microRNA therapeutic product in the United States.

Our strategy

We are the leading biopharmaceutical company focused on the discovery and development of first-in-class drugs based on our proprietary microRNA product platform. The key elements of our strategy are to (i) build a meaningful clinical portfolio by advancing our current clinical programs and rapidly advancing our preclinical programs into clinical development; (ii) focus our resources on developing drugs for oncology indications or orphan diseases where the development and commercialization activities are appropriate for our size and financial resources; (iii) selectively form strategic alliances to augment our expertise and accelerate development and commercialization; (iv) develop microRNA biomarkers to support our therapeutic product candidates; and (v) maintain our scientific and intellectual leadership in the microRNA field.

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

In April 2008, we formed a strategic alliance with GSK to discover and develop microRNA therapeutics for immuno-inflammatory diseases. In February 2010, we and GSK expanded the alliance to include potential microRNA therapeutics for the treatment of HCV. In June 2013, we amended our agreement with GSK and agreed that RG-101 was fully-owned by us and that miR-122 would remain a collaboration target under the agreement. Effective January 2015, this strategic alliance was terminated.

In June 2010, we formed a strategic alliance with Sanofi to discover and develop microRNA therapeutics for fibrotic diseases. In July 2012, we expanded the alliance to include potential microRNA therapeutics in oncology. The original research term for this strategic alliance expired in June 2013, upon which we and Sanofi entered into an option agreement pursuant to which we granted Sanofi an exclusive right to negotiate the co-development and commercialization of certain of our unencumbered microRNA programs, for which Sanofi paid us an upfront option fee of \$2.5 million. In addition, Sanofi granted us an exclusive option to negotiate the co-development and commercialization of miR-21. In February 2014, we and Sanofi extended our strategic alliance and Sanofi concurrently made a \$10.0 million investment in our common stock. Under the terms of our extended alliance, Sanofi will have opt-in rights to our RG-012 clinical fibrosis program targeting miR-21 for the treatment of Alport Syndrome, our preclinical program targeting miR-21 for oncology indications, and our preclinical programs targeting miR-221/222 for oncology indications, each of which is to be led by us. If Sanofi chooses to exercise its option on any of these programs, Sanofi will reimburse us for a significant portion of our preclinical and clinical development costs and will also pay us an option exercise fee for any such program, provided that \$1.25 million of the \$2.5 million upfront option fee paid to us by Sanofi in connection with the June 2013 option agreement will be creditable against such option exercise fee. In addition, we will be eligible to receive clinical and regulatory milestone payments under these programs and potentially commercial milestone payments. We also continue to be eligible to receive royalties on microRNA therapeutic products commercialized by Sanofi or will have the right to co-promote these products. For additional information, see Note 5 to our financial statements under Item 8 of Part II of this Annual Report.

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In August 2012, we formed a strategic alliance with AstraZeneca to discover and develop microRNA therapeutics for cardiovascular diseases, metabolic diseases and oncology. In March 2015, we and AstraZeneca nominated RG-125, a GalNAc-conjugated anti-miR 103/107 oligonucleotide that has been shown to improve insulin sensitivity and glucose tolerance in animal models as a clinical development candidate in NASH in patients with type 2 diabetes/pre-diabetes and we earned a \$2.5 million milestone. In December 2015, AstraZeneca commenced the first-in-human dosing of RG-125 (AZD4076) in healthy volunteers and we earned an additional \$10.0 million milestone. AstraZeneca is responsible for further development of RG-125 under our collaboration. Pursuant to this alliance, we previously investigated targeting microRNA-33, or miR-33 for the treatment of atherosclerosis and microRNA-19, or miR-19 in oncology. We and AstraZeneca agreed to terminate these programs as collaboration targets. In addition, AstraZeneca has the right to substitute a new target for miR-33 and miR-19. If products for all three targets are successfully developed and commercialized through pre-agreed sales targets, we could receive additional milestone payments of up to \$485.5 million and would be entitled to receive royalties based on a percentage of net sales of those products. For additional information, see Note 5 to our financial statements under Item 8 of this Annual Report.

In August 2012, we entered into a collaboration agreement with Biogen to evaluate the potential use of microRNA signatures as a biomarker for human patients with multiple sclerosis, or MS. In August 2014, we and Biogen entered into a new collaboration and license agreement to collaborate on microRNA biomarkers for MS and simultaneously terminated the August 2012 collaboration and license agreement. We have completed the research under this collaboration and earned \$3.7 million in payments. Following achievement of the final milestone, which was earned by analyzing the treatment effects of a Biogen relapsing MS drug on circulating microRNA profiles identified by Regulus microMarkers<sup>SM</sup>, the scope of the research to be performed under the current collaboration agreement has concluded.

Under these strategic alliances, we are eligible to receive approximately \$900.0 million in aggregate milestone payments upon successful commercialization of microRNA therapeutics and royalties on net sales for the programs contemplated by our agreements. These payments include up to \$107.8 million upon achievement of preclinical and investigational new drug, or IND, milestones, up to \$128.0 million upon achievement of clinical development milestones, up to \$180.0 million upon achievement of regulatory milestones and up to \$490.0 million upon achievement of commercialization milestones.

### 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. Our objective is to continue to expand our intellectual property estate through our multiple layer approach in order to protect our microRNA therapeutics and to maintain our leading position in the microRNA therapeutics field.

We believe that we have a leading intellectual property position and substantial know-how relating to the development and commercialization of microRNA therapeutics, composed of:

- over 250 patents and patent applications that we own or have in-licensed from academic institutions and third parties including our founding companies, Anylam and Ionis, related to microRNA and microRNA drug products; and
- numerous patents and patent applications exclusively licensed from our founding companies, Anylam and Ionis, related to RNA technologies, including patent and patent applications relating to chemical modification of oligonucleotides that are useful for microRNA therapeutics, including chemical modifications incorporated into our clinical candidates.

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. Based on a typical patent term ending 20 years from the date of filing of the application, patents within this portfolio that have issued or may yet issue would have a statutory expiration date in 2029.

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We have an 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 infection. 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. Based on a typical patent term ending 20 years from the date of filing of the application, patents within this portfolio that have issued or may yet issue would have a statutory expiration date in 2025.

We have an exclusive license from ETH Zürich to patent rights related to the use of anti-miR therapeutics targeting miR-103/107 for the treatment of metabolic disorders, including type 2 diabetes. In collaboration with us, Dr. Markus Stoffel and colleagues demonstrated that inhibition of miR-103/107 in disease models of diabetes and obesity resulted in beneficial phenotypic effects, including improved insulin sensitivity and glucose homeostasis. The ETH Zurich-licensed portfolio includes more than 10 U.S. and foreign patents and patent applications. Based on a typical patent term ending 20 years from the date of filing of the application, patents within this portfolio that have issued or may yet issue would have a statutory expiration date in 2030.

Our portfolio of exclusively and jointly owned patent and patent applications is currently composed of over 150 U.S. and foreign patents and patent applications with claims to compositions-of-matter or methods related to our microRNA drug products and microRNA product platform. We jointly own approximately ten of the patents and pending applications including patents claiming methods for treating liver cancer, including hepatocellular carcinoma, or HCC, using anti-miRs targeting miR-21 and a patent claiming methods for treating liver cancer, including HCC, using a lipid-formulated miR-34a mimic. Based on the patents and patents that may issue from pending applications within our portfolio, patent protection for our microRNA drug products and their methods of use is currently expected to expire between 2024 and 2035.

Our founding companies, Alnylam and Ionis, 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 microRNA field. The technologies covered in these patents and applications include various chemical modifications that are applicable to microRNA therapeutics. Due to patent expiration and strategic patent portfolio decisions, the total number licensed to Regulus will fluctuate from year to year. Among the licensed patents or patent applications, those covering key chemical modifications for use in microRNA drug products are currently expected to expire in 2023, 2027 and 2029.

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 microRNA 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 microRNA sequences, including microRNAs that are the focus of several of our programs. The patent rights encompass the microRNA gene sequences as well as the antisense sequences that are complementary to the microRNAs and thus cover both microRNA mimic and anti-miR products. Our license is co-exclusive with our founding companies, Alnylam and Ionis, 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. Based on a typical patent term ending 20 years from the date of filing of the application, 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, or U.S. PTO, 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 microRNA product candidates and their methods of use.

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In some circumstances we rely, and may continue to rely, 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.

### 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 Ionis, for exclusive use in microRNA therapeutics. In April 2011, we entered into a direct, co-exclusive license with Max-Planck. The license provides to us, Alnylam and Ionis, 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. We made a \$50,000 payment in 2014 related to the initiation of the Phase I clinical trial for RG-101. In 2015, we made a \$50,000 payment related to the initiation of the Phase I study of RG-012 and a \$150,000 payment related to initiation of the Phase II clinical trial for RG-101. 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.

Based on a typical patent term ending 20 years from the date of filing of the application, the longest lived patent rights licensed to us under the agreement have a statutory expiration date of September 2022.

##### Diagnostic license

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 initial payment to Max-Planck of €175,000. In addition, we made annual maintenance payments to Max-Planck of €30,000 in each of 2013, 2014 and 2015, and will continue to make annual maintenance payments in this amount 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 at the 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. Based on a typical patent term ending 20 years from the date of filing of the application, 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. 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

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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 €1.8 million, based upon achievement of specified clinical and regulatory events. In 2014, we paid the University of Würzburg €100,000 related to the initiation of IND-enabling studies for RG-012 and in 2015 we made a €200,000 payment related to the initiation of the Phase I study of RG-012. In the event we initiate a Phase II 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.

Based on a typical patent term ending 20 years from the date of filing of the application, 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 Ionis entered into a co-exclusive license agreement with Stanford, relating to its patent applications claiming the use of anti-miR therapeutics targeting miR-122 to reduce the replication of HCV. Upon our formation, we received access to the Stanford technology as an affiliate of Alnylam and Ionis. In July 2009, Ionis assigned its rights and obligations under the license agreement to us. In December 2014, Alnylam 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 exclusively licensed product which will be payable upon achievement of specified regulatory and clinical milestones in an aggregate amount of up to \$400,000. In 2014, we made a \$50,000 payment to Stanford related to the initiation of the Phase I clinical trial for RG-101. 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.

Based on a typical patent term ending 20 years from the date of filing of the application, the last to expire patent licensed to us under the agreement is currently expected to expire in May 2025.

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ETH Zürich

In May 2010, we entered into an exclusive license agreement with ETH Zürich, relating to its patent applications claiming the use of anti-miR therapeutics targeting miR-103/107 for the treatment of metabolic disorders, including type 2 diabetes.

ETH Zürich has retained 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 the terms of the sublicense agreement include obligations equivalent to those of our license agreement with ETH Zürich.

As a license issuance fee, we paid ETH Zürich CHF 20,000. We must make annual license maintenance payments during the term of the agreement. Patent prosecution costs paid by us are creditable against maintenance payments due the same calendar year, and maintenance payments are creditable against royalty payments made in the same year. We will be required to pay ETH Zürich milestone payments of up to an aggregate of CHF 1.7 million, based on achievement of specified clinical and regulatory events. As of December 31, 2015, we have CHF 100,000 recorded as an accrued payable as a result of AstraZeneca's first patient dosing in a first-in-human Phase I clinical study of RG-125. Upon commercialization of a product, we will be required to pay ETH Zürich 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 diligent and reasonable efforts to develop and commercially exploit a licensed product.

Based on a typical patent term ending 20 years from the date of filing of the application, the last to expire patent licensed to us under the agreement is currently expected to expire in May 2030.

Alnylam/Ionis

In September 2007, we entered into a license and collaboration agreement with Alnylam and Ionis, which we subsequently amended, restated and superseded in January 2009, and further amended in June 2010, October 2011 and August 2013. Under the agreement, we acquired an exclusive, royalty-bearing, worldwide license, with rights to sublicense, to patent rights owned or licensed by Alnylam and Ionis to develop, manufacture and commercialize products covered by the licensed patent rights for use in microRNA compounds which are microRNA antagonists and microRNA therapeutics containing these compounds. In addition, we have certain rights to miR-mimics. Under the agreement, we granted to both Alnylam and Ionis a license to practice our intellectual property developed by us to the extent that it is useful specifically to Alnylam's RNAi programs or Ionis' single-stranded oligonucleotide programs, but not including microRNA compounds or therapeutics that are the subject of our exclusive licenses from Alnylam and Ionis.

We are required to use commercially reasonable efforts to develop and commercialize licensed products under the agreement. We are required to notify Alnylam and Ionis when a program reaches development stage (defined as initiation of good laboratory practices, or GLP, toxicology studies) and whether or not we intend to pursue the program. Under the agreement, both Alnylam and Ionis have an option to assume the development and commercialization of product candidates in a program that we do not pursue. If neither Alnylam nor Ionis exercises this option, we are required to use our best efforts to finalize a term sheet with a third party with respect to such program. In the event we are unable to complete a transaction with a third party, both Alnylam and Ionis have a second opt-in option.

If an election is made by either Alnylam or Ionis (but not both) to opt-in, such party will pay us a one-time fixed payment, the amount of which will depend on whether the first or the second opt-in option was exercised, with a higher amount due if the first opt-in option was exercised. Clinical and regulatory milestones are also payable to us in the event the opt-in election is exercised. Such milestones total \$64.0 million in the aggregate if the election is made during the first opt-in period or \$15.7 million in the aggregate if the election is made at the second opt-in period. Tiered royalties are payable to us as a percentage of net sales on all products commercialized by the opt-in party. These royalties range from the low to middle single digits depending upon the volume of sales. The opt-in party is also entitled to sublicense the development program to a third party. In such a case, we are also entitled to receive a percentage of the sublicense income received by the opt-in party. The percentage payable depends upon the point at

which the opt-in party sublicenses the program and ranges from the low end of the 10 to 20% range to the high end of the 40 to 50% range. The opt-in party is only required to pay the higher of the clinical and regulatory milestones or the sublicense income received in any calendar quarter. The opt-in party is also responsible for all third party payments due under other agreements as a result of the development. In the event both Alnylam and Ionis elect to opt-in during either opt-in period, the parties have agreed to work together to amend the development plan to continue development of the project, including funding of such project and assignment of roles and responsibilities.

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In the event we or one of our strategic alliance partners continues with the development of a program, each of Alnylam and Ionis are entitled to royalties as a percentage of net sales. For products that we independently commercialize, these royalties will be in the low single digits. For products commercialized by a third-party collaborator, the royalties will be either the same percentage of net sales as described above or, if the sublicense does not provide a specified level of royalties to us or upon our election, a percentage of the sublicense income received by us from the strategic alliance partner and a modified royalty. The modified royalty would be based upon the lower of the single digit percentage discussed above or one third of the royalty received by us after payments made by us to third parties for development, manufacture and commercialization activities under other agreements. In addition, if we sublicense rights to a collaborator, we will be required to pay to each of Alnylam and Ionis a percentage of our sublicense income in the mid-single digits. We are also responsible for payments due to third parties under other agreements as a result of our development activities, including payments owed by Alnylam and/or Ionis under their agreements.

Under the October 2011 amendment, Alnylam and Ionis granted us the right to research microRNA mimics under the licensed intellectual property of Alnylam and Ionis. In the event we develop a miR-mimic, we must first obtain approval from Alnylam and/or Ionis, as applicable, and such approval is subject to the consent of applicable third parties, if any. No additional consideration will be owed by us to Alnylam or Ionis for granting approval. We have the right to sublicense our research rights. We granted to both Alnylam and Ionis a fully paid up, worldwide and exclusive license to any intellectual property developed by us and useful to their research programs and which are not microRNA antagonists or approved miR-mimics.

In August 2013, we entered into an amendment to the Amended and Restated License and Collaboration Agreement with Ionis and Alnylam dated January 1, 2009, as amended in June 2010 and October 2011 (as amended, the "Amendment"). Under the terms of the Amendment, the parties agreed to our use of certain Alnylam-controlled intellectual property concerning the use and manufacture of GalNAc conjugates ("GalNAc Process Technology") on a non-exclusive basis. We will generally not be permitted to sublicense or otherwise transfer the GalNAc Process Technology and other Alnylam licensed intellectual property rights relating to GalNAc conjugate technology without the prior written consent of Alnylam, subject to certain limited exceptions for sublicenses to third party collaboration partners. There were no financial terms related to this Amendment. Amounts included in our operating expenses as a result of costs incurred from services provided under the Agreement or out-of-pocket expenses were zero for the years ended December 31, 2015 and 2014 and \$0.6 million for the year ended December 31, 2013.

In February 2015, we entered into a letter agreement with Alnylam Pharmaceuticals, Inc. ("Alnylam") pursuant to which we and Alnylam agreed to the financial terms for certain technology acquired by Alnylam within the licensed patent rights under our Amended and Restated License and Collaboration Agreement (the "Additional Patent Rights") with Alnylam and Ionis. In addition to any royalties payable by us to Alnylam pursuant to the terms of the Amended and Restated License and Collaboration Agreement, we agreed to pay Alnylam an additional low single-digit royalty on net sales of certain products utilizing the Additional Patent Rights, with the exact royalty percentage payable being dependent on the total amount of net sales during the calendar year. We also agreed to pay Alnylam milestone payments on certain products utilizing the additional patent rights of up to \$33.0 million per product upon the achievement of certain regulatory milestone events. There was no activity under this agreement for the year ended December 31, 2015.

The agreement expires on the earlier of the cessation of development of the potential royalty-bearing products prior to the commercial sale of any such products anywhere in the world or following the first commercial sale of such products, the expiration of royalty obligations determined on a country-by-country and product-by-product basis.

### Manufacturing

We contract with third parties to manufacture our compounds and intend to continue to do so in the future. We do not own or operate, nor do we 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.

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### Research and Development Expenses

In 2015, 2014 and 2013, research and development expenses were \$56.4 million, \$41.0 million and \$29.9 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 intellectual property estate and scientific expertise in the microRNA 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 microRNA therapeutics, but any products that we may commercialize will have to compete with existing and new therapies that may become available in the future. In addition, we expect that for each disease category for which we develop and apply our microRNA therapeutics, there are other biotechnology companies that will compete against us by applying marketed products and development programs using technology other than microRNA therapeutics. The key competitive factors that will affect the success of any of our development candidates, if commercialized, are likely to be their efficacy, safety, convenience, price and the availability of reimbursement from government and other third-party payors relative to such competing technologies. Our commercial opportunity could be reduced or eliminated if our competitors have products which are better in one or more of these categories.

### 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;
- 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.

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Before testing any compounds with potential therapeutic value in humans, the drug candidate enters the preclinical study 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 imposes 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 provide oversight for 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 may be 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.

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.

Concurrently 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.

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### 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. If the FDA determines that an NDA is incomplete or is found to be non-navigable, the filing may be refused and must be re-submitted for consideration. 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 from filing in which to complete its initial review of a standard NDA and respond to the applicant, and six months from filing for a priority NDA. The FDA does not always meet its PDUFA goal dates. The review process and the PDUFA goal date may be extended by three months or longer if the FDA requests or the NDA sponsor otherwise provides additional information or clarification regarding information already provided in the submission 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 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 the sponsor and 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 submit new information, 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, which are 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.

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### 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. For example, our RG-012 drug candidate to treat Alport syndrome has received orphan designation in both the United States and Europe. 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 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 has similar but not identical benefits in the European Union.

### Expedited development and review programs

The FDA has several regulatory pathways for expedited development and/or review of products intended to treat serious conditions. These pathways are Fast Track designation, Breakthrough Therapy Designation, accelerated approval, and priority review. These programs do not change the standards for approval but may expedite the development or approval process. Products may meet the standards for consideration under one or more of these pathways.

The Fast Track program is intended to expedite development 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. In addition to more frequent meetings with the FDA to discuss the drug's development plan and ensure collection of appropriate data needed to support drug approval, the FDA will consider for review sections of the NDA on a rolling basis as sections are completed, based on an agreed schedule, and the sponsor pays any required user fees upon submission of the first section of the NDA.

In addition, the FDA has recently established a Breakthrough Therapy designation as part of the FDA Safety and Innovation Act (FDASIA, Section 902), which became law in 2012. Breakthrough Therapy designation is a process designed to expedite the development and review of drugs that are intended to treat a serious condition and where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on or more clinically significant endpoint(s). A drug that receives Breakthrough Therapy designation from the FDA is eligible for all Fast Track designation features, plus intensive guidance on an efficient drug development program beginning as early as Phase 1 and organizational commitment involving senior managers.

Products 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. Accelerated Approval can be granted with restrictions to the marketing and distribution of the product, and the FDA can withdraw marketing approval if the required post-marketing studies fail to show a clinical benefit or if the Sponsor fails to conduct required post-marketing studies.

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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.

### 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 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 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

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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 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 healthcare laws and regulations

In addition to FDA restrictions on marketing of pharmaceutical products, several other types of state and federal healthcare laws and regulations have been applied to restrict certain business practices in the biopharmaceutical industry in recent years. These laws include the following:

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 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. Federal false claims laws, including the federal civil False Claims Act, prohibit 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 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 civil False Claims Act, which state laws apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply

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regardless of the payor. Also, the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created additional federal criminal statutes that prohibit, among other things, knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private third-party payors 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.

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 for Economic and Clinical Health Act, or HITECH, and their implementing regulations, impose on certain types of individuals and entities certain requirements relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's 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.

Further, the federal Physician Payments Sunshine Act, enacted as part of the PPACA, requires certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to report annually to the Centers for Medicare & Medicaid Services, or CMS, information related to payments or other transfers of value made to physicians and teaching hospitals. Applicable manufacturers and applicable group purchasing organizations must also report annually to CMS ownership and investment interests held by the physicians and their immediate family members.

Other state laws and regulations may also apply, such as those that: require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government; and/or state laws that require manufacturers to report information related to transfers of value to healthcare providers or marketing expenditures.

If our operations are found to be in violation of any of the federal and state healthcare laws or regulations 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, disgorgement, contractual damages, reputational harm, diminished profits and future earnings, 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.

For example, the PPACA 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;

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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;

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

an 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, thereby potentially increasing manufacturers' Medicaid rebate liability;

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

new requirements created by the Physician Payments Sunshine Act to report certain financial arrangements with physicians and teaching hospitals, as defined in the PPACA and as further described above;

a requirement to annually report drug samples that manufacturers and distributors provide to physicians;

an 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 has 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.

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 U.S. 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. In addition, under the Consolidated Appropriations Act, 2016, Congress temporarily suspended and/or delayed implementation of certain taxes authorized under the PPACA. 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 U.S. 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.

### Pharmaceutical Coverage, Pricing, and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any product candidates for which we obtain regulatory approval. In the United States and markets in other countries, sales of any products for which we or our collaborators receive regulatory approval for commercial sale will depend, in part, on the extent to which third-party payors provide coverage and establish adequate reimbursement levels for such drug products.

In the United States, third-party payors include federal and state healthcare programs, government authorities, private managed care providers, private health insurers and other organizations. Third-party payors are increasingly challenging the price, examining the medical necessity and reviewing the cost-effectiveness of medical drug products and medical services, in addition to questioning their safety and efficacy. Moreover, the process for determining whether a third-party payor will provide coverage for a drug product may be separate from the process for setting the price of a drug product or for establishing the reimbursement rate that such a payor will pay for the drug product. A payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a drug product does not assure that other payors will also provide coverage for the drug product. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

The marketability of any product candidates for which we receive regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. In addition, emphasis on managed care in the United States has increased and we expect will continue to increase the pressure on



pharmaceutical pricing. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we or our collaborators receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

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### Europe / rest of world government regulation

In addition to regulations in the United States, we and our strategic alliance partners are 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 GCPs 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 from country to country. In all cases, again, the clinical trials are conducted in accordance with GCPs 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, 2015, we had 92 employees, of which 88 were full-time employees. Of these full-time employees, 71 employees are engaged in research and development activities and 17 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.

### 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.

We maintain a website at [www.regulusrx.com](http://www.regulusrx.com), to which we regularly post copies of our press releases as well as additional information about us. Our Annual Reports 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](http://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.

The Regulus Therapeutics logo is a trademark of Regulus Therapeutics Inc. We use "Regulus Therapeutics" as a trademark in the United States and other countries. We have registered this trademark in the United States, the European Union and Switzerland. We use "microMarkers" as a servicemark in the United States and other countries. We

have filed for registration of this servicemark in the United States. This 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,

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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 JOBS Act. 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. References herein to “emerging growth company” shall have the meaning associated with it in the JOBS Act.

### Item 1A. Risk Factors

You should consider carefully the following risk factors, together with all of the other information included 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 biopharmaceutical 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 microRNA product platform, undertaking basic research around microRNA targets and conducting preclinical and clinical studies for our initial programs. We have initiated clinical development of RG-101 and RG-012, and AstraZeneca has initiated clinical development of RG-125 under our strategic alliance, however, we have not yet 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 \$55.7 million, \$56.7 million, and \$18.7 million for the years ended December 31, 2015, 2014 and 2013, respectively. As of December 31, 2015, we had an accumulated deficit of \$191.5 million.

We have devoted most of our financial resources to research and development, including our preclinical and clinical 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 a strategic alliance with Sanofi relating to the development of our miR-21 programs for HCC and kidney fibrosis and our miR-221/222 program for oncology indications and with AstraZeneca to develop metabolic and oncology programs, including development of RG-125 for NASH. Under our agreement with Sanofi, Sanofi has an option to obtain exclusive worldwide licenses for the development, manufacture and commercialization of potential product candidates selected from our programs. If Sanofi exercises its option to obtain a license to develop, manufacture and commercialize any such product candidate, it will assume responsibility for funding and conducting further clinical development and commercialization activities for such product candidate. However, if Sanofi does not exercise its option within the timeframes that we expect, or at all, we will be responsible for funding further development of the applicable product candidate and may not have the resources to do so unless we are able to enter into another strategic alliance for such product candidate. 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 initiated clinical development of RG-101 and RG-012, and AstraZeneca has initiated clinical development of RG-125, however, it will be several years, if ever, before we or our strategic alliance partners have a product candidate ready for commercialization. Even if we or our strategic alliance partners successfully 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 and clinical development of our product candidates, both independently and under our strategic alliance agreements; seek to identify additional microRNA targets and product candidates; acquire or in-

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license other products and technologies; continue with clinical development of 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, regulatory, research and administrative personnel; and create additional infrastructure to support our operations as a publicly traded 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 microRNAs as therapeutic targets;
- completing our research and preclinical development of product candidates;
- initiating and completing clinical trials for product candidates;
- seeking and obtaining marketing approvals for product candidates that successfully complete clinical trials;
- establishing and maintaining supply and manufacturing relationships with third parties;
- launching and commercializing 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 product candidates that we independently develop is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product. 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 capital, which may not be available on acceptable terms, or at all.

Developing pharmaceutical products, including conducting preclinical studies and clinical trials, is expensive. We expect our research and development expenses to substantially increase in connection with our ongoing activities, particularly as we advance our product candidates towards or through clinical trials. We will need to raise additional capital to support our operations and such funding may not be available to us on acceptable terms, or at all.

As we move our lead compounds through toxicology and other preclinical studies, also referred to as nonclinical studies, required to file an IND, and as we conduct clinical development of RG-101, RG-012 and any other future product candidates, we may have adverse results requiring mitigation strategies that may cause us to consume additional capital. Additionally, our strategic alliance partners may not elect to pursue the development and commercialization of any of our microRNA 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 capital or otherwise obtain funding through additional 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.

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:



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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.

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, 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 31st of the preceding 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. In addition, we may grant or provide for the grant of rights to purchase shares of our common stock pursuant to our 2012 Employee Stock Purchase Plan, or the ESPP. The number of shares of our common stock reserved for issuance under the ESPP will automatically increase on January 1 of each calendar year by the lesser of 1% of the total number of shares of our common stock outstanding on December 31st of the preceding calendar year and 500,000 shares, subject to the ability of our board of directors to take action to reduce the size of the increase in any given year. Any such increase, of the maximum amount or a lesser amount, may cause our stockholders to experience additional dilution, which could cause our stock price to fall. Currently, we plan to register the increased number of shares available for issuance under the 2012 Plan and the ESPP each year.

In addition, we have adopted an Inducement Plan pursuant to which our management may grant stock options exercisable for up to an aggregate of 1,000,000 shares of our common stock to new employees as inducements material to such new employees entering into employment with us. The number of shares which may be granted under the Inducement Plan may be increased in the future by our board of directors. In the event we grant options pursuant to our Inducement Plan, our stockholders may experience additional dilution, which could cause our stock price to fall.

**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 microRNA technology, and our future success depends on the successful development of this technology and products based on our microRNA product platform. Neither we nor any other company has received regulatory approval to market therapeutics targeting microRNAs. 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 microRNA 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 microRNA 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.

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The success of our business depends primarily upon our ability to identify, develop and commercialize microRNA 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. Preclinical studies and clinical trials of our product candidates may not be successful. If we are unable to successfully complete preclinical studies 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 development of product candidates that target microRNAs. 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 product candidates.

The success of our 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;
- 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 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 product candidates. Before obtaining marketing approval from regulatory authorities for the sale of product candidates, we or our strategic alliance partners must conduct extensive clinical trials to demonstrate the safety and efficacy of the product candidates in humans. Clinical trials are 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 or other regulatory authorities on final trial design;



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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 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 product candidates beyond those that are currently contemplated, are unable to successfully complete 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 originally 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 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 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 AEs.

If AEs are observed in any clinical trials of our 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;

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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. 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 product candidates, or impose ongoing requirements for potentially costly post-approval studies or post-market surveillance. The holder of an approved 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 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.

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We may not be successful in obtaining or maintaining necessary rights to microRNA 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 microRNA targets. Because our programs may involve a range of microRNA 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 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 may 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 may 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 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 research and development programs and 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 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

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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 microRNA 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 microRNA product candidates. These strategic alliances will likely provide us with limited control over the course of development of a microRNA product candidate, especially once a candidate has reached the stage of clinical development. For example, in our alliance with Sanofi, Sanofi has the option to obtain an exclusive worldwide license to develop, manufacture and commercialize product candidates upon the achievement of relevant endpoints in clinical trials. However, Sanofi is not under any obligation to exercise these options to progress any of our microRNA development candidates. While each of AstraZeneca 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 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, Sanofi may terminate the entire alliance or its current 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. 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 microRNA development candidates or if they terminate the strategic alliance, then, depending on the event:





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- 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 or the 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 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 or the 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 rely on third parties to conduct some aspects of our compound formulation, research and preclinical studies, 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 studies of product candidates. We currently rely and expect to continue to rely on third parties to conduct some aspects of our preclinical studies and formulation development.

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 rely on third-party manufacturers to produce our preclinical and clinical product candidates, and we intend to rely on third parties to produce future clinical supplies of 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 or supply agreements with third parties under commercially reasonable terms;

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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.

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

We have established 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 or miR-221/222 for oncology indications or RG-012 for kidney fibrosis under its strategic alliance with us, Sanofi will be responsible for the manufacture of the product candidates for further 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. AstraZeneca 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 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 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 product candidates or any approved products.

We 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.



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We or our strategic alliance partners 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 have limited influence over their actual performance. We control only certain aspects of our CROs' activities. Nevertheless, we or our strategic alliance partners are responsible for ensuring that each of our clinical trials are 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.

We, our alliance partners and our CROs are required to comply with the FDA's or other regulatory agency's GCPs 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 and other non-U.S. regulatory agencies enforce these GCPs through periodic inspections of trial sponsors, principal investigators and clinical trial sites. If we or our CROs fail to comply with applicable GCPs, the clinical data generated in our 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 GCPs. In addition, our 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 product candidates. As a result, our financial results and the commercial prospects for such products and any product candidates that we develop would be harmed, our costs could increase, and our ability to generate revenues could be delayed.

We also 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 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 patents with claims that cover the products in the United States or in other countries. There is no assurance that all of the potentially relevant prior art relating to our patents and patent applications has been found; such prior art 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. A patent may be challenged through one or more of several

administrative proceedings including post-grant challenges, re-examination or opposition before the U.S. PTO or foreign patent offices. For example, re-examination of, or oppositions to, patents owned by or licensed to us have previously been initiated, and while we believe these concluded proceedings did not result in a commercially relevant impact on the individual patents, any successful challenge of 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.

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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, in certain situations, if we and one or more third parties have filed patent applications in the United States and claiming the same subject matter, an administrative proceeding, known as an interference, can be initiated to determine which applicant is entitled to the patent on that subject matter. Such an interference proceeding 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 a patent or patent application in such a proceeding may not be successful and, even if successful, may result in substantial costs and distract our management and other employees.

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. 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.

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 each of our employees agrees to assign their inventions to us through an employee inventions agreement, 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. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we and our strategic alliance partners are pursuing development candidates. For example, we are aware that Roche Innovation Center Copenhagen (formerly Santaris Pharma A/S) has patents and patent applications in the microRNA therapeutics space, including patents and patent applications related to targeting microRNAs, such as miR-122, for the treatment of disease. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our product candidates may be subject to claims of infringement of the patent rights of third parties.

Third parties may assert that we are employing their proprietary technology without authorization. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our product candidates. Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in patents that our 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 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



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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 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 microRNA 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 Ionis, provide us with rights to nucleotide technologies in the field of microRNA therapeutics based on oligonucleotides that modulate microRNAs. 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 Ionis 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 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 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.

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.

Our defense in a litigation 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.

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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 programs that are part of our strategic alliance agreements with Sanofi and AstraZeneca will depend in large part on the development and marketing efforts of our alliance partners. If our alliance partners are unable or unwilling 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 or when Sanofi or AstraZeneca elects to pursue the development and commercialization of any of the microRNA 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, 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 material breach by Sanofi or AstraZeneca, we have the right to assume the responsibility at our own expense for the development of the applicable microRNA 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 microRNA product candidates and our business could be materially and adversely affected. Further, under certain circumstances, we may owe Sanofi 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. Our competitors may 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.

Most of our programs 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 microRNA 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.

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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 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 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 adequate 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 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. For example, we have co-promotion rights with Sanofi with respect to our miR-21 and miR-221/222 programs, but would need to build our sales, marketing, managerial and other non-technical capabilities in order to effectively carry out co-promotion activities with respect to any approved products that are developed through these programs. With respect to certain of our current programs that are the subject of existing strategic alliances, such as the metabolic and oncology programs 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 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.



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Our current and future strategic alliance partners, if any, may not dedicate sufficient resources to the commercialization of our 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 product candidates to healthcare professionals and in geographical regions, including the United States, that will 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.

Under our strategic alliance agreements with Sanofi and AstraZeneca, they will be responsible for the commercialization of future product candidates, if any, from their respective programs, as applicable. If any other 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 product candidates, which could make it difficult for us to sell products profitably.

Market acceptance and sales of any 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, government payors 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 available for any future product candidates. Also, inadequate reimbursement amounts may reduce the demand for, or the price of, our future products. Further, one payor's determination to provide coverage for a product does not assure that other payors will also provide coverage for the product. If reimbursement is not available, or is available only at limited levels, we may not be able to successfully commercialize 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 payors 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





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

As of December 31, 2015, we had 88 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 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. We intend to relocate our corporate headquarters and research facility to a new facility in the first half of 2016. If we are unable to transition our technology, personnel and operations in a cost-efficient and timely manner, we may experience disruptions that negatively impact our business, objectives, financial condition and results of operations. Moreover, 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 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-

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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.

Certain current and future relationships with customers and third party payors as well as certain of our business operations 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 United States, our operations may be directly, or indirectly through our customers, further 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 healthcare laws and regulations that may affect our ability to operate include:

the federal Anti-Kickback Statute, which prohibits, among other things, persons and entities 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;

federal civil and criminal false claims laws and civil monetary penalty laws, including the civil False Claims Act, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment to the federal government, including Medicare or Medicaid, that are false or fraudulent;

the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created additional federal criminal statutes that prohibit, among other things, 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 for Economic and Clinical Health Act of 2009, or HITECH, and their implementing regulations, which imposes certain requirements on certain types of individuals and entities relating to the privacy, security and transmission of individually identifiable health information;

the federal Physician Payments Sunshine Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to report annually to the Centers for Medicare & Medicaid Services, or CMS, information related to payments or other transfers of value made to physicians, and further requires applicable manufacturers and applicable group purchasing organizations to report annually to CMS ownership and investment interests held by physicians and their immediate family members; 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 payor, including commercial insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government; state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; 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

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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, disgorgement, imprisonment, contractual damages, reputational harm, diminished profits and future earnings, and curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

Recent and future healthcare legislation may further impact our business operations.

The United States and some foreign jurisdictions are considering or have enacted a number of legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our products profitably. Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality or expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives.

By way of example, in March 2010, the PPACA was signed into law, intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add transparency requirements for the healthcare and health insurance industries, impose taxes and fees on the health industry and impose additional health policy reforms. Among the provisions of the ACA of importance to our potential product candidates are:

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

an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13.0% of the average manufacturer price for branded and generic drugs, respectively;

a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected;

extension of a manufacturer's 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 certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;

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

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

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

We expect that the PPACA, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and lower reimbursement, and in additional downward pressure on the price that we receive for any approved product. Any reduction in reimbursement from Medicare or other government-funded

programs may result in a similar reduction in payments from private payors.

There have been judicial and Congressional challenges and amendments to certain aspects of the PPACA, and we expect there will be additional challenges and amendments to the PPACA in the future. Moreover, we cannot predict what healthcare reform initiatives may be adopted in the future. Further federal, state and foreign legislative and regulatory developments are likely, and we expect ongoing initiatives to increase pressure on drug pricing. Such reforms could have an adverse effect on anticipated revenues from product candidates that we may successfully develop and for which we may obtain regulatory approval and may affect our overall financial condition and ability to develop product candidates.

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

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The use of our 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 current and 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 product candidates; and
- decreased demand for our product candidates, if approved for commercial sale.

We maintain product liability insurance relating to the use of our therapeutics in clinical trials. However, such insurance coverage 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 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 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.

Cyber security risks and the failure to maintain the confidentiality, integrity, and availability of our computer hardware, software, and Internet applications and related tools and functions could result in damage to our reputation and/or subject us to costs, fines or lawsuits.

Our business requires manipulating, analyzing and storing large amounts of data. In addition, we rely on a global enterprise software system to operate and manage our business. We also maintain personally identifiable information about our employees. Our business therefore depends on the continuous, effective, reliable, and secure operation of our computer hardware, software, networks, Internet servers, and related infrastructure. To the extent that our hardware or software malfunctions or access to our data by internal research personnel is interrupted, our business could suffer. The integrity and protection of our employee and company data is critical to our business and employees have a high expectation that we will adequately protect their personal information. The regulatory environment governing information, security and privacy laws is increasingly demanding and continues to evolve. Maintaining compliance with applicable security and privacy regulations may increase our operating costs. Although our computer and communications hardware is protected through physical and software safeguards, it is still vulnerable to fire, storm, flood, power loss, earthquakes, telecommunications failures, physical or software break-ins, software viruses, and similar events. These events could lead to the unauthorized access, disclosure and use of non-public information. The techniques used by criminal elements to attack computer systems are sophisticated, change frequently and may originate from less regulated and remote areas of the world. As a result, we may not be able to address these techniques proactively or implement adequate preventative measures. If our computer systems are compromised, we could be subject to fines, damages, litigation and enforcement actions, and we could lose trade secrets, the occurrence of which could harm our business. In addition, any sustained disruption in internet access provided by other companies could harm our 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**



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The market price of our common stock may be highly volatile.

Since shares of our common stock were sold in our initial public offering in October 2012 at a price of \$4.00 per share, our closing stock price as reported on The NASDAQ Global Market has ranged from \$4.15 to \$22.08, through February 19, 2016. The trading price of our common stock is likely to continue to be volatile.

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 studies or clinical trials;
- inability to obtain additional funding;
- any delay in filing an IND or NDA for any of our 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 product candidates;
- changes in laws or regulations applicable to our preclinical and clinical development activities, product candidates or future products;
- inability to obtain adequate product supply for our 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;
- 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 beneficially own a majority of our stock and will be able to exert significant control over matters subject to stockholder approval.

As of February 19, 2016, our executive officers, directors, 5% stockholders and their affiliates beneficially owned a majority 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.

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We are an “emerging growth company,” and the reduced reporting requirements applicable to emerging growth companies could make our common stock less attractive to investors.

We are currently an “emerging growth company,” as defined in the JOBS Act. As 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 through December 31, 2017, although we may lose that status sooner. 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.

The requirements of being a publicly traded company may strain our resources and divert management’s attention. As a publicly traded 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 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. As an “emerging growth company” we are permitted to implement many of these requirements over a longer period and up to five years from the pricing of our initial public offering. We have taken 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.

If our existing stockholders sell, or indicate an intention to sell, substantial amounts of our common stock in the public market, the trading price of our common stock could decline. In addition, shares of common stock that are either subject to outstanding options or reserved for future issuance under our employee benefit plans are or may become eligible for sale in the public market to the extent permitted by the provisions of various vesting schedules and Rule 144 under the Securities Act. If these additional shares of common stock are sold, or if it is perceived that they will be sold, in the public market, the trading price of our common stock could decline.

Certain holders of our securities are entitled to rights with respect to the registration of their shares under the Securities Act. 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. Pursuant to our registration statements on Form S-3 which became effective in April 2014 and in April 2015, up to 7,190,422 shares held by certain of our stockholders remain available for resale thereunder. We may file additional registration statements in the future to provide for the further sale of shares of common stock by our stockholders. Any further sales of securities by these stockholders could have a material adverse effect on the

trading price of our common stock.

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

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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. Pursuant to our registration statement on Form S-3 that became effective on April 16, 2014, we may sell up to \$18.2 million of common stock or warrants from time to time in one or more public offerings. On April 8, 2015, we filed a shelf registration statement on Form S-3, which we subsequently amended on February 23, 2016 and which is currently effective. Under the shelf registration statement, as amended, we may offer to sell from time to time in one or more offerings shares of our common stock in an aggregate amount of up to \$150 million. 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. In addition, we may file additional registration statements in the future to provide for the further sale of shares of common stock by us or by selling stockholders.

Pursuant to our 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 preceding 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. In addition, we may grant or provide for the grant of rights to purchase shares of our common stock pursuant to the ESPP. The number of shares of our common stock reserved for issuance under the ESPP will automatically increase on January 1 of each calendar year by the lesser of 1% of the total number of shares of our common stock outstanding on December 31 of the preceding calendar year and 500,000 shares, 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 and ESPP each year. Pursuant to our Inducement Plan, our management is authorized to grant stock options exercisable for up to an aggregate of 1,000,000 shares of our common stock to new employees as inducements material to such new employees entering into employment with us. The number of shares which may be granted under the Inducement Plan may be increased in the future by our board of directors.

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 triggered an "ownership change" limitation at the completion of our initial public offering in October 2012 and again in July 2015. 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:

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- 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;
- 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;
- establishing the state of Delaware as the sole forum for certain legal actions against the Company, its officers and directors; 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 are located in San Diego, California and includes approximately 29,000 square feet of leased space.

In October 2015, we provided written notice to our landlord of our election to early terminate the lease agreement between us and BMR-John Hopkins Court LLC, or BMR, dated March 19, 2010, as amended. The lease provided an early termination right for approximately 21,500 square feet of the total leased premises after the 60th month of the lease, provided at least 9 months prior written notice. The effective date of termination of this portion of the lease is June 30, 2016. We will not incur any material early termination penalties as a result of our termination of that portion of the lease. The remaining 7,500 square feet of office and laboratory space did not provide for early termination rights and will expire in June 2017.

In July 2015 we entered into a new lease agreement with Walton Torrey Owner B, L.L.C. for the lease of approximately 59,000 square feet of office and laboratory space in San Diego, California for a term of 96 months from the lease commencement date, and anticipate moving the Company's headquarters in the first half of 2016.

Item 3. Legal Proceedings

None.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

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

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## Market Information

Our common stock is traded on The NASDAQ Global Market under the symbol "RGLS." 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 periods indicated.

	Price Range	
	High	Low
Year Ended December 31, 2014:		
First Quarter	\$ 11.88	\$ 6.76
Second Quarter	\$ 9.24	\$ 5.40
Third Quarter	\$ 8.32	\$ 6.13
Fourth Quarter	\$ 25.60	\$ 6.23
Year Ended December 31, 2015:		
First Quarter	\$ 21.22	\$ 13.75
Second Quarter	\$ 18.83	\$ 9.80
Third Quarter	\$ 11.59	\$ 6.30
Fourth Quarter	\$ 10.60	\$ 5.85

## Holders of Record

As of February 19, 2016, there were approximately 11 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.

## 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, 2015 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.

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## Item 6. Selected Financial Data

The selected financial data set forth below is derived from our audited financial statements, including the balance sheets at December 31, 2015 and 2014 and the related statements of operations for each of the three years ended December 31, 2015 and related notes appearing elsewhere in this Annual Report. The balance sheet data as of December 31, 2013, 2012 and 2011 and the statement of operations data for the years ended December 31, 2012 and 2011 are derived from our audited financial statements that are not included in this Annual Report. 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.

Statement of operations data	Year ended December 31,				
	2015	2014	2013	2012	2011
Revenue under strategic alliances and collaborations	\$20,759	\$7,669	\$19,569	\$12,700	\$13,767
Loss from operations	(54,758 )	(44,910 )	(17,802 )	(12,574 )	(7,137 )
Net loss	\$(55,748 )	\$(56,680 )	\$(18,668 )	\$(17,408 )	\$(7,602 )
Net loss per share, basic and diluted	\$(1.08 )	\$(1.29 )	\$(0.49 )	\$(2.12 )	\$(85.82 )
	As of December 31,				
Balance sheet data	2015	2014	2013	2012	2011
Cash, cash equivalents and short-term investments*	\$115,319 *	\$159,743	\$114,005	\$98,100	\$38,144
Working capital	121,626	129,759	106,812	86,161	25,816
Total assets	141,083	171,480	123,065	103,518	42,881
Convertible note payable, at fair value	—	23,397	11,279	10,134	10,815
Convertible preferred stock	—	—	—	—	42,691
Accumulated deficit	(191,515 )	(135,767 )	(79,087 )	(60,419 )	(43,011 )
Total stockholders’ equity (deficit)	124,078	132,014	93,457	62,093	(41,494 )

\*Includes \$1.3 million of restricted cash as of December 31, 2015.

## 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.”

## OVERVIEW

We are a biopharmaceutical company focused on discovering and developing first-in-class drugs that target microRNAs to treat a broad range of diseases. We were formed in 2007 when Alnylam Pharmaceuticals, Inc. and Ionis Pharmaceuticals, Inc. (formerly Isis Pharmaceuticals, Inc.) contributed significant intellectual property, know-how and financial and human capital to pursue the development of drugs targeting microRNAs pursuant to a license and collaboration agreement. We have established strategic alliances with AstraZeneca AB and Sanofi to discover, develop and commercialize microRNA therapeutics. Under these strategic alliances, we are eligible to



receive approximately \$900.0 million in aggregate milestone payments upon successful commercialization of microRNA therapeutics and royalties on net sales for the programs contemplated by our agreements. These payments include up to \$107.8 million upon achievement of preclinical and investigational new drug, or IND, milestones, up to \$128.0 million upon achievement of clinical development milestones, up to \$180.0 million upon achievement of regulatory milestones and up to \$490.0 million upon achievement of commercialization milestones.

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microRNAs are naturally occurring ribonucleic acid, or RNA, molecules that play a critical role in regulating key biological pathways. Scientific research has shown that the improper balance, or dysregulation, of microRNAs is directly linked to many diseases. To date, approximately 500 microRNAs have been identified in humans, each of which is believed to interact with a specific set of genes that control key aspects of cell biology. Since most diseases are multi-factorial and involve multiple targets in a pathway, the ability to modulate gene networks by targeting a single microRNA provides a new therapeutic approach for treating complex diseases.

RNA plays an essential role in the process used by cells to encode and translate genetic information from DNA to proteins. RNA is comprised of subunits called nucleotides and is synthesized from a DNA template by a process known as transcription. Transcription generates different types of RNA, including messenger RNAs that carry the information for proteins in the sequence of their nucleotides. In contrast, microRNAs are RNAs that do not code for proteins but rather are responsible for regulating gene expression by affecting the translation of target messenger RNAs. By interacting with many messenger RNAs, a single microRNA can regulate several genes that are instrumental for the normal function of a biological pathway.

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

- microRNAs, until recently, have not been a focus of pharmaceutical research;
- microRNAs play a critical role in regulating biological pathways by controlling the translation of many target genes;
- microRNA therapeutics target entire disease pathways which may result in more effective treatment of complex multi-factorial diseases; and
- microRNA therapeutics may be synergistic with other therapies because of their different mechanism of action.

We believe we have assembled the leading position in the microRNA field, including expertise in microRNA biology and oligonucleotide chemistry, a broad intellectual property estate, relationships with key opinion leaders and a disciplined drug discovery and development process. We refer to these assets as our microRNA product platform. We are using our microRNA product platform to develop chemically modified, single-stranded oligonucleotides that we call anti-miRs to modulate microRNAs and return diseased cells to their healthy state. We believe microRNAs may be transformative in the field of drug discovery and that anti-miRs may become a new and major class of drugs with broad therapeutic application, much like small molecules, biologics and monoclonal antibodies. In addition to our microRNA product platform, we have established Regulus microMarkers<sup>SM</sup>, a division focused on identifying microRNAs as biomarkers of human disease to support our therapeutic pipeline, collaborators and strategic partners. Regulus microMarkers<sup>SM</sup> utilizes a clinically-validated, highly reproducible technology platform to identify microRNAs as potential biomarkers for disease and we control key intellectual property and know-how related to the division. We believe that microRNA biomarkers may be used to select optimal patient segments in clinical trials and to monitor disease progression or relapse. We believe these microRNA biomarkers can be applied toward drugs that we develop and drugs developed by other companies with which we partner or collaborate. We have completed a research collaboration with Biogen focused on the discovery of microRNAs as biomarkers for multiple sclerosis and have also completed research for another leading, commercial-stage pharmaceutical company to explore microRNAs as biomarkers for specific patient populations. We also maintain several academic research collaborations focused on the identification of microRNAs as biomarkers in multiple disease areas.

### ‘Clinical Map Initiative’ Goals

To advance our microRNA therapeutics pipeline and biomarkers platform over the next several years, we have outlined specific goals under our ‘Clinical Map Initiative’ strategy. We are developing RG-101, a GalNAc-conjugated anti-miR targeting miR-122, a host factor for the hepatitis C virus, or HCV, infection. In addition, we are developing RG-012, an anti-miR targeting microRNA-21 for the treatment of Alport syndrome, a life-threatening kidney disease driven by genetic mutations with no approved therapy. We are also advancing several programs toward clinical development in areas such as oncology and fibrosis, both independently and with our strategic alliance partners AstraZeneca and Sanofi. Under our strategic alliance with AstraZeneca, AstraZeneca recently commenced clinical development of RG-125, a GalNAc-conjugated anti-miR targeting microRNA-103/107 for the treatment of nonalcoholic steatohepatitis, or NASH, in patients with type 2 diabetes/pre-diabetes.

RG-101: In August 2015, we initiated a Phase II study investigating RG-101 designed to evaluate a shortened, four-week treatment regimen containing a subcutaneous administration of 2 mg/kg of RG-101 at Day 1 and Day 29, in combination with oral direct-acting antiviral agents Harvoni®, Olysio®, and Daklinza® for 28 days. In February, 2016, we announced interim results from the clinical study. Thirty-eight patients had been evaluated through 8 weeks of follow up. Ninety-seven percent of those patients (37/38) had HCV RNA viral load measurements below the limit of quantification. For those patients through 12 weeks of follow-up, 100% remained below the limit of quantification (14/14). To date, RG-101 has been generally well

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tolerated with the majority of adverse events considered mild or moderate (headache and fatigue most commonly reported, each at approximately 11%), two SAEs reported during the follow-up period, and with no study discontinuations. The primary endpoint analysis (12 week follow up) for all 79 patients in the study are anticipated to be reported in second quarter of 2016. To expand the potential development of RG-101, in November 2015 we entered into a clinical trial collaboration and formulation agreement with GSK LLC. In the first quarter of 2016, we plan to initiate a Phase II study evaluating the potential to achieve sustained viral responses post treatment with a single subcutaneous administration of RG-101 in combination with daily oral administrations of GSK2878175, a non-nucleoside NS5B polymerase inhibitor, for up to 12 weeks in treatment-naïve patients chronically infected with HCV genotypes 1 and 3. Concurrently, GSK will work on developing a long-acting parenteral formulation for injection (“LAP”) of GSK2878175 which could improve patient compliance through reduced dosing intervals and potentially extend opportunities for HCV therapeutic intervention. This LAP formulation of GSK2878175 may be used in potential additional clinical trials together with RG-101 following completion of the planned Phase II study. Neither we nor GSK has any further obligations or commitments beyond the contemplated study under the clinical trial collaboration agreement.

RG-012: In June 2015, we initiated a Phase I study to evaluate the safety, tolerability and pharmacokinetics of subcutaneous dosing of RG-012 in healthy volunteers and the study is now complete. Forty healthy volunteer subjects were enrolled in this first-in-human, single ascending dose study. RG-012 was well-tolerated and there were no serious adverse events reported. We also continue to enroll Alport syndrome patients in our global ATHENA natural history of disease study, which is designed to characterize the natural decline of renal function (as measured by established renal markers) in Alport syndrome patients over time. We believe the data from the ATHENA study will provide the clinical basis for the design of a Phase II proof-of-concept study to monitor the therapeutic effect of RG-012 on the decline in renal function in patients with Alport syndrome. We plan to initiate a Phase II proof-of-concept study evaluating the efficacy of RG-012 in Alport syndrome patients during 2016.

RG-125: AstraZeneca initiated a Phase I study evaluating RG-125 in humans in December 2015, earning Regulus a \$10.0 million milestone from the collaboration. AstraZeneca is responsible for all future development for RG-125.

**FINANCIAL OPERATIONS OVERVIEW**

**Revenue**

Our revenues generally consist of upfront payments for licenses or options to obtain licenses in the future, milestone payments and payments for other research services under strategic alliance and collaboration agreements.

In the future, we may generate revenue from a combination of license fees and other upfront payments, payments for research and development services, 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, if at all, of preclinical, clinical, regulatory and commercialization milestones, 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 development of our therapeutic programs, and our Regulus microMarkers<sup>SM</sup> division. 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, contract manufacturing organizations, or CMOs, other clinical trial related vendors, consultants and our scientific advisors;
- license fees; and
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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.

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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.

To date, we have conducted research on many different microRNAs 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 therapeutic areas of focus. Our organization is structured to allow the rapid deployment and shifting of resources to focus on the best known targets based on our ongoing research. As a result, in the early phase of our development programs, our research and development costs are not tied to any specific target. However, we are currently spending the majority of our research and development resources on our clinical development programs.

Since our conversion to a corporation in January 2009, we have grown from 15 research and development personnel to 71 and have spent a total of approximately \$194.2 million in research and development expenses through December 31, 2015.

We expect our research and development expenses to increase for the foreseeable future as we continue to conduct our ongoing clinical studies, initiate additional clinical studies and advance our pre-clinical research programs toward the clinic, including other IND-enabling activities. The process of conducting clinical trials and pre-clinical studies 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 clinical data, pre-clinical data, competition, manufacturing capability and commercial viability. Under our strategic alliance with Sanofi, we are responsible for the development of product candidates through proof-of-concept, after which time Sanofi would be responsible for the costs of clinical development and commercialization and all related costs, in the event it exercises its option to such program. 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 acceptance of an IND application (or its foreign equivalent) 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.

Successful development of future product candidates 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 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, Sarbanes-Oxley compliance and other accounting fees and directors' and officers' liability insurance premiums.

Other income (expense), net

Other income (expense) consists primarily of interest income and expense, and various income or expense items of a non-recurring nature. We earn interest income from interest-bearing accounts and money market funds for cash and cash equivalents and marketable securities, such as interest-bearing bonds, for our short-term investments. Interest expense has historically represented interest payable under the convertible note payable and equipment and tenant

improvement financing arrangements. We recorded periodic gains and losses from changes in value of a convertible note payable until its conversion into common stock in January 2015.

**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

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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, milestone payments and payments for other research services under strategic alliance and collaboration agreements. We recognize revenues when all four of the following criteria are met: (1) persuasive evidence of 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.

Multiple element arrangements, such as our strategic alliance agreements with Sanofi and AstraZeneca and our former collaboration agreement with Biogen Inc. are analyzed to determine whether the deliverables within the agreement can be separated or whether they must be accounted for as a single unit of accounting. 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. If the delivered element does not have stand-alone value, 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.

### Milestones

We apply the milestone method of accounting to recognize revenue from milestone payments when earned, as evidenced by written acknowledgement from the collaborator or other persuasive evidence that the milestone has been achieved and the payment is non-refundable, provided that the milestone event is substantive. A milestone event is defined as an event (i) that 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; (ii) for which there is substantive uncertainty at the inception of the arrangement that the event will be achieved; and (iii) that would result in additional payments being due to us. Events for which the occurrence is either contingent solely upon the passage of time or the result of a counterparty’s performance are not considered to be milestone events. A milestone event is substantive if all of the following conditions are met: (i) the consideration is commensurate with either our performance to achieve the milestone, or the enhancement of the value to the delivered item(s) as a result of a specific outcome resulting from our performance to achieve the milestone; (ii) the consideration relates solely to past performance; and (iii) the consideration is reasonable relative to all the deliverables and payment terms (including other potential milestone consideration) within the arrangement.

We assess whether a milestone is substantive at the inception of each arrangement. If a milestone is deemed non-substantive, we will account for that milestone payment using a method consistent with the related units of accounting for the arrangement over the related performance period.

### Deferred Revenue

Amounts received prior to satisfying the above revenue recognition criteria are recorded as deferred revenue in the accompanying balance sheets. Amounts not expected to be recognized within the next 12 months are classified as non-current deferred revenue.

### Clinical Trial Accrual

We make estimates of our accrued expenses as of each balance sheet date in our financial statements based on the facts and circumstances known to us at that time. Our accrued expenses for pre-clinical studies and clinical trials are based on estimates of costs incurred and fees that may be associated with services provided by clinical trial investigational sites, clinical research organizations (“CROs”) and for other clinical trial-related activities. Payments



under certain contracts with such parties depend on factors such as successful enrollment of patients, site initiation and the completion of clinical trial milestones. In accruing for these services, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If possible, we obtain information regarding unbilled services directly from these service providers. However, we may be required to estimate these services based on other information available to us. If we underestimate or

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overestimate the activities or fees associated with a study or service at a given point in time, adjustments to research and development expenses may be necessary in future periods. Historically, our estimated accrued liabilities have approximated actual expense incurred. Subsequent changes in estimates may result in a material change in our accruals.

**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.

• 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. The balance of our convertible note payable, which was valued under the fair value option, was converted into shares of common stock in January 2015.

Our significant accounting policies and estimates are more fully described in Note 1 to our financial statements included elsewhere in this Annual Report.

**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 included elsewhere in this Annual Report.

**RESULTS OF OPERATIONS**

Comparison of the years ended December 31, 2015 and 2014

The following table summarizes our results of operations for the years ended December 31, 2015 and 2014 (in thousands):

	Years ended	
	December 31,	
	2015	2014
Revenue under strategic alliances and collaborations	\$20,759	\$7,669
Research and development expenses	56,387	41,046
General and administrative expenses	19,130	11,533
Loss from changes in valuation of convertible note payable	(1,811	) (12,118
Revenue under strategic alliances and collaborations		

Our revenues are generated from ongoing strategic alliance and collaborations, and generally consist of upfront payments for licenses or options to obtain licenses in the future, milestone payments and payments for other research services. The following table summarizes our total revenues for the periods indicated (in thousands):

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	Years ended	
	December 31,	
	2015	2014
AstraZeneca	\$18,871	\$1,859
Sanofi	71	979
GSK	—	3,509
Biogen	1,817	1,122
Other	—	200
Total revenues under strategic alliances and collaborations	\$20,759	\$7,669

Revenue under strategic alliances and collaborations was \$20.8 million for the year ended December 31, 2015 compared to \$7.7 million for the year ended December 31, 2014.

Revenue under the AstraZeneca collaboration and license agreement increased to \$18.9 million for the year ended December 31, 2015 compared to \$1.9 million for the year ended December 31, 2014. In January 2015, we and AstraZeneca entered into a letter agreement pursuant to which we agreed to perform additional research and development activities and to provide manufacturing support for RG-125. Revenue of \$4.5 million was recognized under the letter agreement for the year ended December 31, 2015. In March 2015, we earned a \$2.5 million preclinical milestone payment for the clinical candidate selection of RG-125, a GalNAc-conjugated anti-miR targeting microRNA-103/107 for the treatment of NASH in patients with type 2 diabetes/pre-diabetes. In December 2015, we earned a \$10.0 million clinical milestone payment upon AstraZeneca's first patient dosing in a first-in-human Phase I clinical study of RG-125. AstraZeneca is responsible for all future development of RG-125.

In February 2014, we and Sanofi entered into a second amended and restated collaboration and license agreement to renew our strategic alliance to discover, develop and commercialize microRNA therapeutics to focus on specific orphan disease and oncology targets. Revenue recognized from our strategic alliance with Sanofi was \$0.1 million for the year ended December 31, 2015 compared to \$1.0 million for the year ended December 31, 2014. Revenue recognized in these periods reflected the amortization of payments received from Sanofi over our estimated period of performance.

In August 2014, we and Biogen entered into a new collaboration and license agreement to collaborate on microRNA biomarkers for MS. Revenue recognized from our agreement with Biogen increased to \$1.8 million for the year ended December 31, 2015 compared to \$1.1 million for the year ended December 31, 2014. This increase was primarily a result of amortization of the \$2.0 million upfront payment received in August 2014 which was recognized over the estimated period of performance, ending in September 2015. In January 2015, May 2015 and September 2015, we earned research milestone payments under the August 2014 collaboration and license agreement of \$0.1 million, \$0.3 million, and \$0.3 million, respectively.

Revenue recognized from our product development and commercialization agreement with GSK decreased to zero for the year ended December 31, 2015 compared to \$3.5 million for the year ended December 31, 2014. In October 2014, we received written notice from GSK of its election to terminate the product development and commercialization agreement. The effective date of the termination was January 15, 2015.

As of December 31, 2015, we had \$3.3 million of deferred revenue, which consisted of payments received through our strategic alliances that have not yet been recognized in accordance with our revenue recognition policies.

#### Research and development expenses

Research and development expenses were \$56.4 million for the year ended December 31, 2015, compared to \$41.0 million for the year ended December 31, 2014. This change was primarily driven by a net increase in our aggregate pre-clinical studies and clinical trial program costs of \$8.3 million for the year ended December 31, 2015, compared to the year ended December 31, 2014. Specifically, clinical trial costs for RG-101 increased by \$6.4 million for the year ended December 31, 2015 compared to the year ended December 31, 2014. This increase was due to costs incurred associated with the Phase II study for RG-101. Pre-clinical study costs for RG-125 increased by \$4.3 million for the year ended December 31, 2015 compared to the year ended December 31, 2014. This increase was due to costs incurred associated with additional research and development activities and product manufacturing to support the initiation of a Phase I clinical study. This increase was partially offset by a decrease in clinical trial costs for RG-012

of \$2.4 million for the year ended December 31, 2015 compared to the year ended December 31, 2014.

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Research and development personnel costs, including stock based compensation, increased by \$5.1 million for the year ended December 31, 2015 compared to the year ended December 31, 2014. This was principally driven by an increase in non-cash stock-based compensation expense of \$4.1 million for the year ended December 31, 2015 compared to the year ended December 31, 2014. In June 2015, we incurred a non-recurring severance charge of \$1.3 million associated with the resignation of our former chief scientific officer, including \$0.9 million of non-cash stock-based compensation expense. We expect our research and development expenses to increase for the foreseeable future as we continue to conduct our ongoing clinical studies, initiate additional clinical studies and advance our pre-clinical research programs toward the clinic, including other IND-enabling activities.

General and administrative expenses

General and administrative expenses were \$19.1 million for the year ended December 31, 2015 compared to \$11.5 million for the year ended December 31, 2014. This change was primarily driven by an increase in personnel costs, including non-cash stock based compensation, of \$5.6 million for the year ended December 31, 2015 compared to the year ended December 31, 2014. In June 2015, we incurred a non-recurring severance charge of \$3.3 million associated with the resignation of our former chief executive officer, including \$2.3 million of non-cash stock-based compensation expense. In December 2015, we incurred a non-recurring severance charge of \$1.0 million associated with the resignation of our former chief business officer, including \$0.7 million of non-cash stock-based compensation expense. In addition, changes in general and administrative expenses were due to increases in external service costs and other operating expenses associated with general business activities of \$2.0 million for the year ended December 31, 2015 compared to the year ended December 31, 2014.

Gain/loss from valuation of convertible note payable

We recorded a loss from changes in value of the convertible note payable of \$1.8 million for the year ended December 31, 2015 compared to a loss of \$12.1 million for the year ended December 31, 2014. Changes in value were driven by changes in our stock price during the respective periods. In January 2015, the convertible note payable was converted into 1,356,738 shares of our common stock at a conversion price of \$4.00 per share.

Comparison of the years ended December 31, 2014 and 2013

The following table summarizes the results of our operations for the periods indicated (in thousands):

	Years ended December 31,	
	2014	2013
Revenue under strategic alliances and collaborations	\$7,669	\$19,569
Research and development expenses	41,046	29,942
General and administrative expenses	11,533	7,429
Loss from change in valuation of convertible note payable	(12,118	) (1,145

Revenue under strategic alliances and collaborations

The following table summarizes our total revenues for the periods indicated (in thousands):

	Years ended December 31,	
	2014	2013
AstraZeneca	\$1,859	\$1,859
Sanofi	979	15,336
GSK	3,509	1,778
Biogen	1,122	596
Other	200	—
Total revenues under strategic alliances and collaborations	\$7,669	\$19,569

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Revenue under strategic alliances and collaborations was \$7.7 million for the year ended December 31, 2014 compared to \$19.6 million for the year ended December 31, 2013.

Revenue recognized from our strategic alliance with Sanofi decreased to \$1.0 million for the year ended December 31, 2014, compared to \$15.3 million in 2013. Revenue recognized under the second amended and restated collaboration and license agreement was \$0.1 million for the year ended December 31, 2014. In June 2013, the research term expired under the Sanofi alliance, at which time we entered into an option agreement. In July 2013, we received an upfront payment of \$2.5 million, of which \$1.25 million is creditable against future amounts payable by Sanofi to us and therefore will be deferred until its application to a creditable transaction. The non-creditable portion of this payment, \$1.25 million, was recognized as revenue over the option period from the effective date of the option agreement in June 2013 through the expiration of the option period, resulting in \$0.1 million and \$1.2 million in revenue recognized for the years ended December 31, 2014 and 2013, respectively. In conjunction with the expiration of the original research term in June 2013 and subsequent option agreement, we re-evaluated our estimated period of performance and recognized the remaining \$10.1 million in deferred revenue associated with the initial upfront payment of \$25.0 million ratably from June 2013 through the expiration of the option period in January 2014, resulting in \$0.8 million and \$14.1 million in revenue recognized for the years ended December 31, 2014 and 2013, respectively.

Revenue recognized from our product development and commercialization agreement with GSK increased to \$3.5 million for the year ended December 31, 2014, compared to \$1.8 million in 2013. In October 2014, we received written notice from GSK of its election to terminate the product development and commercialization agreement. Concurrent with the notice of termination, we recognized the remaining \$3.1 million in deferred revenue associated with the 2008 upfront payment, as our estimated period of performance was complete. In June 2013, the agreement with GSK was amended to state that RG-101, and other formulations thereof, would be developed by us independently of our alliance with GSK for the treatment of chronic HCV infection. As a result, we recognized the remaining \$1.1 million in deferred revenue associated with the 2010 upfront payment, as our estimated period of performance was complete.

Revenue recognized from our collaboration and license agreement with Biogen increased to \$1.1 million for the year ended December 31, 2014, compared to \$0.6 million in 2013, primarily due to amortization of \$0.8 million of the \$2.0 million upfront payment received under the new collaboration and license agreement.

Revenue from our other strategic alliances was materially consistent for the years ended December 31, 2014 and 2013.

### Research and development expenses

Research and development expenses increased to \$41.0 million for the year ended December 31, 2014 compared to \$29.9 million for the year ended December 31, 2013. The change was primarily driven by Phase 1 clinical study costs for RG-101 and an increase in IND-enabling activities for RG-012 of \$7.4 million. Salaries and related benefits, including stock based compensation, increased by \$3.1 million due to an increase in employees engaged in research and development activities to 65 as of December 31, 2014, compared to 59 as of December 31, 2013.

### General and administrative expenses

General and administrative expenses increased to \$11.5 million for the year ended December 31, 2014 compared to \$7.4 million for the year ended December 31, 2013. The increase was primarily driven by an increase in salaries and related benefits, including stock based compensation, of \$2.8 million, in addition to external service costs and other general operating expenses of \$1.3 million associated with the growth of the business and other costs associated with general business activities.

### Loss from change in value of convertible note payable

We recorded a loss from changes in value of convertible note payable of \$12.1 million and \$1.1 million in the statements of operations and comprehensive loss for the years ended December 31, 2014 and 2013, respectively. Changes in value were primarily driven by fluctuations in our stock price.

## LIQUIDITY AND CAPITAL RESOURCES

Since our inception through December 31, 2015, we have received \$75.1 million principally from upfront payments, research funding and preclinical milestones from our strategic alliances and collaborations, \$257.1 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, \$45.8 million in net proceeds from our public offering in July 2013, and \$76.3 million in net proceeds from our public offering in November 2014.

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As of December 31, 2015, we had \$115.3 million in cash, cash equivalents and short-term investments, including \$1.3 million in restricted cash. The following table shows a summary of our cash flows for the years ended December 31, 2015 and 2014 (in thousands):

	Years ended December 31,		
	2015	2014	2013
Net cash (used in) provided by:			
Operating activities	\$(49,859 )	\$(39,510 )	\$(28,330 )
Investing activities	21,475	(29,207 )	(40,889 )
Financing activities	7,017	88,237	46,474
Total	\$(21,367 )	\$19,520	\$(22,745 )

**Operating activities**

Net cash used in operating activities increased to \$49.9 million for the year ended December 31, 2015, compared to \$39.5 million and \$28.3 million for the years ended December 31, 2014 and December 31, 2013, respectively.

Increases in cash used in operating activities have been attributable, in part, to net losses of \$55.7 million, \$56.7 million and \$18.7 million for the years ended December 31, 2015, 2014 and 2013, respectively. Adjustments for non-cash charges, including stock-based compensation and changes in value of our convertible note payable, decreased to \$20.3 million for the year ended December 31, 2015, compared to \$22.3 million for the year ended December 31, 2014. Adjustments for non-cash charges for the year ended December 31, 2013 was \$7.4 million. Changes in working capital resulted in net cash used in operating activities of \$14.5 million, \$5.1 million, and \$17.0 million for the years ended December 31, 2015, 2014 and 2013, respectively. These changes primarily relate to the timing of upfront payments and milestones, compared to the period of revenue recognition.

**Investing activities**

Net cash provided by or used in investing activities for the periods presented primarily related to the net of purchases, sales and maturities of investments used to fund the day-to-day needs of our business. We invest cash in excess of our immediate operating requirements with staggered investment duration or maturity to optimize our return on investment while satisfying our liquidity needs. Net sales and maturities of investments was \$22.9 million for the year ended December 31, 2015, compared to net purchases of investments of \$28.0 million and \$40.1 million for the years ended December 31, 2014 and 2013, respectively. Net cash used for purchases of property and equipment was \$1.4 million, \$1.1 million, and \$0.8 million for the years ended December 31, 2015, 2014 and 2013, respectively.

**Financing activities**

Net cash provided by financing activities was \$7.0 million, \$88.2 million and \$46.5 million for the years ended December 31, 2015, 2014 and 2013, respectively. In 2015, financing activities included proceeds from the exercise of common stock options of \$6.7 million. In 2014, financing activities included a public offering that resulted in net proceeds of approximately \$76.3 million and net proceeds from the issuance of additional common stock of \$12.1 million. In 2013, financing activities included a public offering that resulted in net proceeds of approximately \$45.8 million.

**Future Capital Requirements**

As of December 31, 2015 we had approximately \$115.3 million in cash, cash equivalents and short-term investments, including \$1.3 million in restricted cash. We expect our research and development expenses to substantially increase in connection with our ongoing activities, particularly as we advance our product candidates in or towards clinical programs.

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 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 product candidates;
- the number and characteristics of product candidates that we pursue;



the outcome, timing and cost of regulatory approvals;  
delays that may be caused by changing regulatory requirements;

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- 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.

We believe our cash, cash equivalents and short term investments are sufficient to fund our anticipated operating and capital requirements for, at a minimum, the next twelve months.

**CONTRACTUAL OBLIGATIONS AND COMMITMENTS**

The following is a summary of our long-term contractual obligations as of December 31, 2015 (in thousands):

	Payments due by period				
	Total	2016 <1 year	2017-2018 2-3 years	2019-2020 4-5 years	>5 years
Operating lease obligations relating to facility(1)	\$21,698	\$1,699	\$4,905	\$5,387	\$9,707
Annual maintenance fees for license agreements	888	101	203	203	381
Total	\$22,586	\$1,800	\$5,108	\$5,590	\$10,088

(1) We lease approximately 29,000 square feet for office and laboratory space in San Diego, California under an operating lease agreement. The agreement provided for an early termination option on approximately 21,500 square feet of office and laboratory space, which we exercised. The effective date of early termination is June 30, 2016. The agreement pertaining to the remaining 7,500 square feet of space will expire in June 2017. We entered into a new operating lease agreement in July 2015 for approximately 59,000 square feet of office and laboratory space in San Diego, California, for a term of 96 months from the lease commencement date, and anticipate moving our corporate headquarters in the first half of 2016. Obligations under all lease agreements are included in the above table.

**Off-Balance Sheet Arrangements**

As of December 31, 2015, we did not have any off-balance sheet arrangements.

**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 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

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rates were to have occurred on December 31, 2015, this change would not have had a material effect on the fair value of our investment portfolio as of that date.

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Item 8. Financial Statements and Supplementary Data

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, 2015 and 2014, and the related statements of operations and comprehensive loss, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2015. 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, 2015 and 2014, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2015, in conformity with U.S. generally accepted accounting principles.

/s/ Ernst & Young LLP

San Diego, California

February 23, 2016

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Regulus Therapeutics Inc.

## BALANCE SHEETS

(in thousands, except share and per share data)

	December 31,	
	2015	2014
Assets		
Current assets:		
Cash and cash equivalents	\$15,960	\$37,327
Short-term investments	98,103	122,416
Restricted cash	1,256	—
Contract and other receivables	10,021	274
Prepaid expenses	8,159	4,192
Other current assets	759	742
Total current assets	134,258	164,951
Property and equipment, net	5,400	3,568
Intangibles, net	1,081	1,150
Other assets	344	1,811
Total assets	\$141,083	\$171,480
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	\$2,717	\$2,188
Accrued liabilities	6,329	4,402
Accrued compensation	2,392	2,108
Current portion of deferred revenue	1,194	3,097
Convertible note payable, at fair value	—	23,397
Total current liabilities	12,632	35,192
Deferred revenue, less current portion	2,065	3,252
Other long-term liabilities	2,308	1,022
Total liabilities	17,005	39,466
Commitments and Contingencies (Note 8)		
Stockholders' equity:		
Common stock, \$0.001 par value; 200,000,000 shares authorized, 52,669,266 and 48,944,530 shares issued and outstanding at December 31, 2015 and 2014, respectively	53	49
Additional paid-in capital	315,673	267,929
Accumulated other comprehensive loss	(133	) (197
Accumulated deficit	(191,515	) (135,767
Total stockholders' equity	124,078	132,014
Total liabilities and stockholders' equity	\$141,083	\$171,480
See accompanying notes to these financial statements.		

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Regulus Therapeutics Inc.

## STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS

(In thousands, except share and per share data)

	2015	2014	2013
Revenues:			
Revenue under strategic alliances and collaborations	\$20,759	\$7,669	\$19,569
Total revenues	20,759	7,669	19,569
Operating expenses:			
Research and development	56,387	41,046	29,942
General and administrative	19,130	11,533	7,429
Total operating expenses	75,517	52,579	37,371
Loss from operations	(54,758	) (44,910	) (17,802
Other income (expense):			
Interest and other income	855	388	292
Interest and other expense	(52	) (39	) (36
Loss from valuation of convertible note payable	(1,811	) (12,118	) (1,145
Loss before income taxes	(55,766	) (56,679	) (18,691
Income tax benefit (expense)	18	(1	) 23
Net loss	\$(55,748	) \$(56,680	) \$(18,668
Other comprehensive loss:			
Unrealized gain (loss) on short-term investments, net	64	(181	) 36
Comprehensive loss	\$(55,684	) \$(56,861	) \$(18,632
Net loss per share, basic and diluted	\$(1.08	) \$(1.29	) \$(0.49
Weighted average shares used to compute basic and diluted net loss per share	51,411,353	44,090,165	38,479,447

See accompanying notes to these financial statements.

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## STATEMENTS OF STOCKHOLDERS' EQUITY

(in thousands, except share data)

	Common stock		Additional paid-in capital	Accumulated other comprehensive income (loss)	Accumulated deficit	Total stockholders' equity
	Shares	Amount				
Balance at December 31, 2012	35,831,808	\$36	\$122,528	\$ (52 )	\$ (60,419 )	\$62,093
Issuance of common stock upon exercise of options	732,483	1	593	—	—	594
Stock-based compensation expense	—	—	3,422	—	—	3,422
Issuance of common stock under Employee Stock Purchase Plan	48,035	—	201	—	—	201
Issuance of common stock, net of \$434 of offering costs	5,175,000	5	45,774	—	—	45,779
Unrealized gain on short-term investments	—	—	—	36	—	36
Net loss	—	—	—	—	(18,668 )	(18,668 )
Balance at December 31, 2013	41,787,326	\$42	\$172,518	\$ (16 )	\$ (79,087 )	\$93,457
Issuance of common stock upon exercise of options	1,006,515	1	2,232	—	—	2,233
Stock-based compensation expense	—	—	7,039	—	—	7,039
Issuance of common stock under Employee Stock Purchase Plan	38,085	—	283	—	—	283
Issuance of common stock in private placement	1,303,780	1	9,568	—	—	9,569
Issuance of common stock, net of \$347 of offering costs	4,808,824	5	76,289	—	—	76,294
Unrealized loss on short-term investments	—	—	—	(181 )	—	(181 )
Net loss	—	—	—	—	(56,680 )	(56,680 )
Balance at December 31, 2014	48,944,530	\$49	\$267,929	\$ (197 )	\$ (135,767 )	\$132,014
Issuance of common stock upon exercise of options	2,298,618					