Regulus Therapeutics Inc.
Form 10-K
March 03, 2017
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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 10-K

(Mark One)
x ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
FOR THE FISCAL YEAR ENDED DECEMBER 31, 2016
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 (State or Other Jurisdiction of Incorporation or Organization)	26-4738379 (I.R.S. Employer Identification No.)
10614 Science Center Drive San Diego, CA (Address of Principal Executive Offices)	92121 (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 ý
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 ý
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 ý 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 ý 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. ý

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 ý

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 ý

As of June 30, 2016, 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 $152.6 million, based on the closing price of the registrant's common stock on the NASDAQ Global Market on June 30, 2016 of $2.89 per share.

The number of outstanding shares of the registrant's common stock, par value $0.001 per share, as of February 24, 2017 was 52,932,405.

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 2017 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 May 1, 2017.

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PART I

Forward-Looking Statements

This Annual Report on Form 10-K and the documents incorporated by reference herein 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 of any programs or product candidates that are subject to our collaboration and license agreements with such partners;
- our ability to attract collaborators with relevant 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;
- the accuracy of our estimates regarding future 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. (“Alnylam”) and Ionis Pharmaceuticals, Inc. ("Ionis") 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 an imbalance, or dysregulation, of microRNAs is directly linked to many diseases. To date, over 500 microRNAs have been identified in humans, each of which bind to multi messenger RNAs (mRNA) that control key aspects of cell biology. Since many diseases are multi-factorial, involving multiple targets and

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pathways, the ability to modulate multiple pathways 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 modulating the translation of target messenger RNAs. By interacting with many messenger RNAs, a single microRNA can regulate multiple genes involved in 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 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;
- microRNA therapeutics may be synergistic with other therapies because of their different mechanism of action; and
- microRNAs are a relatively new area of biological research for the industry.

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 are using our microRNA expertise to develop chemically modified, single-stranded oligonucleotides that we call anti-miRs to modulate dysregulated microRNAs and return them to their healthy state. We believe microRNAs may play a critical role in complex disease and that targeting them with anti-miRs may become a source of a new and major class of drugs with broad therapeutic application, much like small molecules, biologics and monoclonal antibodies. We have established strategic alliances with AstraZeneca AB and Sanofi to discover, develop and commercialize microRNA therapeutics.

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.

Development Stage Pipeline

We currently have three programs in clinical development. Our most advanced program, RG-101, is a GalNAc-conjugated anti-miR targeting miR-122, a host factor for the hepatitis C virus, or HCV, infection. Our second program, under our strategic alliance with Sanofi, is RG-012, an anti-miR targeting microRNA-21 for the treatment of Alport syndrome, a life-threatening kidney disease driven by genetic mutations, currently with no approved therapy available. Our third program, under our strategic alliance with AstraZeneca, is RG-125(AZD4076), a GalNAc-conjugated anti-miR targeting microRNA-103/107 for the treatment of non-alcoholic fatty liver disease, or NAFLD, in patients with type II diabetes/pre-diabetes. In late 2016, we nominated two new programs for clinical development from our research pipeline. RGLS5040, an anti-miR targeting microRNA-27 for the treatment of cholestatic disease, is anticipated to be in clinical development after an IND or equivalent regulatory filing in the second half of 2017. RGLS4326, an anti-miR targeting microRNA-17 for the treatment of autosomal dominant polycystic kidney disease, or AKPKD, is anticipated to be in clinical development after an IND or equivalent regulatory filing in the second half of 2017 as well.

RG-101: We are currently evaluating RG-101 in several Phase I/II studies.

- In August 2015, we initiated a Phase II study investigating RG-101 in 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 one of

three oral direct-acting antiviral agents Harvoni®, Olysio®, and Daklinza® for 28 days. In March 2017, we reported top-line results from the primary endpoint analysis of its completed Phase II study of RG-101 in combination with 4 weeks of once/daily approved anti-viral agents Harvoni®, Olysio®, or Daklinza™. The study enrolled 79 treatment naïve genotype 1 and 4 HCV patients (Harvoni® combination arm, n=27, Olysio® combination arm, n=27, Daklinza™ combination arm, n=25). The results from this final analysis demonstrated significant virologic response through 48

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weeks of follow-up: RG-101 plus Harvoni demonstrated 100% SVR48; RG-101 plus Olysio demonstrated 77% SVR48; and RG-101 plus Daklinza™ demonstrated 84% SVR48. There were 10 relapses: six in the Olysio® combination arm (weeks 8, 20, 24 and 32); and four in the Daklinza™ combination arm (weeks 8, 12 and 24). RG-101 in combination with four weeks of oral DAA therapy was generally well tolerated with the majority of adverse events (AE) considered mild or moderate with no AE-related discontinuations. Commonly reported AEs included fatigue, headache, and injection site reactions. There were four patients across all arms that experienced AEs of asymptomatic transient hyperbilirubinemia (greater than or equal to two times the upper limit of normal). No cases met criteria for Hy's law. Over the course of the one-year study, five subjects reported serious adverse events (SAE). As previously reported, there was a single SAE of jaundice in a patient at seven weeks in the Daklinza™ combination arm of the study. Since the interim analysis in June 2016, there were two additional SAEs: one was a trauma-related knee injury and the other was an upper respiratory infection.

- In November 2015, we entered into a clinical trial collaboration and formulation agreement with GSK LLC. In the first quarter of 2016, we initiated 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 initiated the development of a long-acting injectable formulation, or LAI, of GSK2878175, which could improve patient compliance through reduced dosing intervals and potentially extend opportunities for HCV therapeutic intervention. The goal of the development of an LAI formulation in combination with RG-101 would be to create a curative regimen that could be administered to a patient via one or two injections in one visit. We anticipate trial completion in the fourth quarter of 2017.

- In May 2016, we expanded the clinical trial collaboration agreement with GSK to conduct a multi-centered, randomized, dose-ranging Phase II study evaluating the combination of RG-101 and GSK's LAI formulation of GSK2878175 as a potential single-visit cure in patients chronically infected with HCV. This combination study has not yet been initiated. As with the initial collaboration, both parties will contribute to the costs associated with the study. Neither we nor GSK has any further obligations or commitments to each other beyond this expanded clinical collaboration agreement.

- In January 2016, we initiated a multi-center, open label, non-randomized Phase I study to compare the safety, tolerability, pharmacokinetics, and pharmacodynamics of 2 mg/kg of RG-101 in subjects with severe renal insufficiency or end-stage renal disease (ESRD) to healthy control subjects, and further explore RG-101 in hepatitis C infected subjects with severe renal insufficiency or ESRD. The Phase I study has three treatment arms (n=24): (i) healthy volunteers (n=8); (ii) patients with severe renal impairment or ESRD (n=8); and (iii) HCV patients with severe renal impairment or ESRD (n=8). Enrollment was completed in the second quarter of 2016, and the trial was completed in the first quarter of 2017.

- In June 2016, we received verbal notice from the U.S. Food and Drug Administration, or FDA, that our IND for RG-101 for the treatment of chronic HCV infection had been placed on clinical hold. The FDA initiated the clinical hold after a second patient experienced an SAE of jaundice. This SAE occurred in an HCV patient with end-stage renal disease on dialysis enrolled in our on-going Phase I US study 117 days after receiving a single dose of RG-101. In July 2016, we received a formal clinical hold letter from the FDA requesting the following from us: detailed safety data analysis from preclinical and clinical studies; exploration of potential mechanisms of hepatoxicity in non-clinical models; review and input from independent hepatotoxicity experts; additional PK data from the US Phase I study; and a risk/benefit assessment for the proposed therapeutic regimen containing RG-101. In December 2016, we submitted a complete response to the FDA's initial request for information, which included identification of a potential mechanism of hyperbilirubinemia. The Company also submitted a proposal to mitigate this risk. In January 2017, the Company received written communication from the FDA that the clinical development program for RG-101 remains on clinical hold. The FDA has requested the final safety and efficacy data from on-going RG-101 clinical and preclinical studies before reconsidering the clinical hold. These data will be available once the current study protocols are complete

through 48 weeks of follow up, which is anticipated in the fourth quarter of 2017. The FDA also requested additional expert review of liver safety data in light of the proposed mechanism of hyperbilirubinemia. We plan to work diligently with the FDA to seek the release of the clinical hold. Initiation of new RG-101 clinical studies are suspended pending resolution of the FDA clinical hold.

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RG-012: In 2015, we completed a Phase I study to evaluate the safety, tolerability and pharmacokinetics of subcutaneous dosing of RG-012 in healthy volunteers. 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 disease-related decline of renal function (as measured by established blood markers for renal function) in these patients over time. The data from the ATHENA study provided 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.

- In late 2016, in order to address study design comments from European regulators, a Phase I multiple-ascending dose (MAD) study in healthy volunteers was initiated (six-week repeat dosing) to determine safety, PK and other parameters prior to chronic dosing in patients. These data will help inform the final study design for the HERA study, an international randomized, double-blind, placebo-controlled, multi-center Phase II clinical trial designed to evaluate the safety, pharmacodynamics, pharmacokinetics, dose selection, and preliminary efficacy of chronic RG-012 treatment in approximately 30 patients with Alport syndrome. We anticipate the MAD study will be completed in the first half of 2017.

- In March 2017, we modified the Phase II RG-012 clinical development program in patients with Alport syndrome to accelerate patient enrollment and potentially achieve early proof of mechanism/proof of concept. The Phase II program will include the HERA study, and, in parallel, a separate Phase I/II renal biopsy study in Alport patients will be initiated to evaluate RG-012 tissue PK, target engagement of miR-21 and effects on downstream genomic markers of disease. Both studies are anticipated to begin enrollment following the completion of the Phase I MAD study in Q2 2017. Based on projected enrollment rates, data from the renal biopsy study are expected in Q4 2017 and interim data from HERA are expected in mid-2018.

RG-125(AZD4076): In the third quarter of 2016, AstraZeneca initiated a Phase I/IIa, randomized, single-blind, placebo-controlled, multiple ascending dose study in subjects with Type II diabetes and NAFLD. This study is anticipated to be complete in December 2017. Previously, AstraZeneca initiated a Phase I study evaluating RG-125(AZD4076) in healthy volunteers in December 2015, earning us a $10.0 million milestone from the collaboration. Regulus is eligible to receive its next milestone for the collaboration upon AstraZeneca's initiation of Phase IIb. AstraZeneca is responsible for all future development for RG-125(AZD4076).

RGLS5040: In November 2016, we nominated RGLS5040 as a clinical candidate targeting microRNA-27 (miR-27) for the treatment of cholestatic diseases. IND-enabling activities are currently underway in anticipation of filing an IND in the second half of 2017.

RGLS4326: In December 2016, we nominated RGLS4326 as a clinical candidate targeting microRNA-17 (miR-17) for the treatment of ADPKD. IND-enabling activities are currently underway in anticipation of filing an IND in the second half of 2017.

Preclinical Pipeline

We are advancing our preclinical portfolio towards clinical development in renal, hepatic, and central nervous system diseases both independently and with our strategic alliance partners Sanofi and AstraZeneca, and nominated 2 clinical candidates in the fourth quarter of 2016.

Our microRNA product platform

We are the leading company in the field of microRNA therapeutics and are uniquely positioned to leverage oligonucleotide technologies developed by us and our founding companies.

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;

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- a leading microRNA intellectual property estate with over 300 patents and patent applications covering compositions and therapeutic uses related to microRNA and microRNA drug products, as well as access to numerous 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;
- 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 significant unmet medical need and commercial opportunity.

Step 2 - Identification of microRNA targets

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.

Our 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

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focus our own resources on proprietary product opportunities in therapeutic areas where development and commercialization activities are appropriate for our size and financial resources. 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.

*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 a biopharmaceutical company focused on discovering and developing 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 indications that represent significant unmet medical need and 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 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 and 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(AZD4076), 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 NAFLD 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 commenced dosing patients in a Phase IIa clinical trial in the third quarter of 2016. AstraZeneca is responsible for further development of RG-125(AZD4076) 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 August 2016, the research period under the collaboration reached its natural conclusion. As such, AstraZeneca's rights to any other targets from the collaboration expired. If RG-125(AZD4076) is successfully developed and commercialized through certain sales levels, we would be entitled to receive additional milestone payments of up to $160.0 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.

- AstraZeneca is responsible for further development of RG-125(AZD4076) 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 August 2016, the research period under the collaboration reached its natural conclusion. As such, AstraZeneca's rights to any other targets from the collaboration expired. If RG-125(AZD4076) is successfully developed and commercialized through certain sales levels, we would be entitled to receive additional milestone payments of up to $160.0 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.

Under these strategic alliances, we are eligible to receive approximately $590 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 $105.3 million upon achievement of preclinical and investigational new drug, or IND, milestones, up to $57.5 million upon achievement of clinical development milestones, up to $180.0 million upon achievement of regulatory milestones and up to $247.5 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 300 patents and patent applications that we own or have in-licensed from academic institutions and third parties including our founding companies, Alnylam and Ionis, related to microRNA and microRNA drug products; and
- numerous patents and patent applications exclusively licensed from our founding companies, Alnylam 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 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 2029.

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 15 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.

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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 200 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 2036.

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.

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.

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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. As of December 31, 2016, we have recorded a $150,000 payable related to the initiation of the Phase II clinical trial for RG-012. 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 2016, 2015 and 2014 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 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

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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. As of December 31, 2016, we have recorded a €200,000 payable related to the initiation of the Phase II 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.

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.

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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. In April 2016, we paid ETH Zurich CHF 100,000 as a result of AstraZeneca's first patient dosing in a first-in-human Phase I clinical study of RG-125(AZD4076). As of December 31, 2016, we have recorded a CHF 200,000 payable as a result of AstraZeneca’s first patient dosing in a Phase IIa clinical study of RG-125(AZD4076). 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.

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

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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, 2016, 2015 and 2014.

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, 2016.

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.

Research and Development Expenses

In 2016, 2015 and 2014, research and development expenses were $64.3 million, $56.4 million and $41.0 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

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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.

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

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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 direct 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.

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

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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 acceptance of filing in which to complete its initial review of a standard NDA and respond to the applicant, and six months from acceptance of 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.

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

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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.

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.

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

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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 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,

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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 ACA, which, among other things, amended 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 ACA 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 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.

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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 ACA, 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 ACA includes measures to significantly change the way healthcare is financed by both governmental and private insurers. Among the provisions of the ACA of greatest importance to the pharmaceutical and biotechnology industry are the following:

- an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs, that began in 2011;
- an increase in the rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13% of the average manufacturer price for branded and generic drugs, respectively;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts to negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D;
- 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;

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

In January 2017, Congress voted to adopt a budget resolution for fiscal year 2017, the Budget Resolution, that authorizes the implementation of legislation that would repeal portions of the ACA. The Budget Resolution is not a law, however, it is widely viewed as the first step toward the passage of legislation that would repeal certain aspects of the ACA. As a result, there is significant uncertainty regarding future healthcare reform and its impact on our operations.

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.

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 in the United States is

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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, 2016, we had 97 employees. Of these employees, 77 employees are engaged in research and development activities and 20 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 in San Diego, California and our telephone number is (858) 202-6300.

We maintain a website at 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. 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 registered 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, 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.

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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 recently nominated RGLS5040 for the treatment of cholestasis and RGLS4326 for the treatment of ADPKD. We have initiated clinical development of RG-101 and RG-012, and AstraZeneca has initiated clinical development of RG-125(AZD4076) 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 $81.8 million, $55.7 million, and $56.7 million for the years ended December 31, 2016, 2015 and 2014, respectively. As of December 31, 2016, we had an accumulated deficit of $273.4 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, through our secured term loan from Oxford Finance, LLC, or Oxford, 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 continue the clinical development of RG-125(AZD4076) for NAFLD. 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 IND-enabling activities for RGLS5040 and RGLS4326. We have also initiated clinical development of RG-101 and RG-012, and AstraZeneca has initiated clinical development of RG-125(AZD4076), 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-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;

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- 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 RGLS5040 and RGLS4326 and any other future 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:

- 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.

Payments under the instruments governing our indebtedness may reduce our working capital. In addition, a default under our loan and security agreement could cause a material adverse effect on our financial position.

In June 2016, we entered into a loan and security agreement with Oxford. Under the terms of the loan agreement, Oxford initially provided us with a Term A Loan of $20.0 million, with an additional $10.0 million Term B Loan available to us upon the achievement of a milestone until the earlier of 60 days after the achievement of the milestone or March 31, 2017, subject to the non-occurrence of a prior event of default. Our obligations under the loan agreement

are secured by a first priority security

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interest in substantially all of our current and future assets, other than our intellectual property. We have also agreed not to encumber our intellectual property assets, except as permitted by the loan agreement. All of the Term Loans mature on June 1, 2020 and will be interest-only through June 1, 2018, followed by 24 equal monthly payments of principal and unpaid accrued interest. Payments under the loan agreement could result in a significant reduction of our working capital.

The loan agreement requires us, and any debt arrangements we may enter into in the future may require us, to comply with various covenants that limit our ability to, among other things:

- dispose of assets;
- complete mergers or acquisitions;
- incur indebtedness;
- encumber assets;
- pay dividends or make other distributions to holders of our capital stock;
- make specified investments; and
- engage in transactions with our affiliates.

These restrictions could inhibit our ability to pursue our business strategies. If we default under our obligations under the loan agreement, the lender could proceed against the collateral granted to it to secure our indebtedness or declare all obligation under the loan agreement to be due and payable. In certain circumstances, procedures by the lenders could result in a loss by us of all of our equipment and inventory, which are included in the collateral granted to the lenders. If any indebtedness under the loan agreement were to be accelerated, there can be no assurance that our assets would be sufficient to repay in full that indebtedness. In addition, upon any distribution of assets pursuant to any liquidation, insolvency, dissolution, reorganization or similar proceeding, the holders of secured indebtedness will be entitled to receive payment in full from the proceeds of the collateral securing our secured indebtedness before the holders of other indebtedness or our common stock will be entitled to receive any distribution with respect thereto. We may incur additional indebtedness in the future. The debt instruments governing such indebtedness may contain provisions that are as, or more, restrictive than the provisions governing our existing indebtedness under the loan agreement. If we are unable to repay, refinance or restructure our indebtedness when payment is due, the lenders could proceed against the collateral or force us into bankruptcy or liquidation.

RISKS RELATED TO THE DISCOVERY AND DEVELOPMENT OF PRODUCT CANDIDATES

The FDA has placed a clinical hold on RG-101, our most advanced compound under development, after a second patient experienced a serious adverse event of jaundice in our on-going Phase I study for the treatment of chronic HCV infection. Our business may be adversely affected if the clinical hold cannot be favorably resolved in a timely manner or if such regulatory concerns lead to more burdensome preclinical or clinical studies that cause significant delays or expense in developing our product candidates.

In June 2016, the FDA placed a full clinical hold on our RG-101 clinical program after a second patient experienced an SAE of jaundice. This SAE occurred in a HCV patient with end-stage renal disease on dialysis enrolled in our on-going Phase I U.S. study 117 days after receiving a single dose of RG-101. In accordance with the clinical hold, the FDA provided that no new dosing with RG-101 could be initiated in the United States. In July 2016, we received a formal clinical hold letter from the FDA requesting the following from us: detailed safety data analysis from preclinical and clinical studies; exploration of potential mechanisms of hepatoxicity in non-clinical models; review and input from independent hepatotoxicity experts; additional PK data from the US Phase I study; and a risk/benefit assessment for the proposed therapeutic regimen containing RG-101. In December 2016, we submitted a complete response to the FDA's initial request for information, which included identification of a potential mechanism of hyperbilirubinemia. We also submitted a proposal to mitigate this risk. In January 2017, the FDA informed us that the full clinical hold placed on our RG-101 clinical development program in June 2016 will remain in effect pending the FDA’s review of certain preclinical and clinical information to be submitted by us to the FDA, including a final preclinical study safety report for RG-101, final efficacy and safety data from certain clinical trials of RG-101, additional expert opinion of liver safety data in light of the proposed mechanism of hyperbilirubinemia, and an updated risk/benefit assessment of the proposed therapeutic regimens using RG-101. We currently anticipate submitting a complete response to the FDA with the requested information in the fourth quarter of 2017. However, as

we depend upon our contract research organizations to timely complete and report the preclinical and clinical studies, we may be delayed in submission of a complete response if our CROs cannot meet our current deadlines or if data reveals other unanticipated issues.

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We cannot be certain whether or when the FDA will lift the clinical hold and allow us to pursue further development of RG-101 in the United States. If we are unable to cause the clinical hold to be completely lifted in a timely manner, our development timelines and our business may be further adversely affected and our stock price may further decline. Further, even if the FDA lifts the clinical hold, the FDA or other regulatory agencies may continue to express safety concerns after the hold is lifted, and future preclinical or clinical studies involving RG-101 or combination regimens that include RG-101 may be more burdensome or include additional preclinical or clinical endpoints that are difficult to meet. In such instances, our progress in the development of this program may be significantly slowed and the associated costs may be significantly increased, adversely affecting our business and may potentially cause us to cease development of this program entirely.

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.

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;

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- 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;
- imposition of a clinical hold 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 protocol procedures or requirements, 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

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- 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;
- 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

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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.

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.

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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 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;

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- 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:

- 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 candidate subject to the AstraZeneca agreement or the product candidates subject to 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

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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, including risks that we would not be subject to 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;
- 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.

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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 the product candidate it took into clinical trials under its strategic alliance with us and we will face similar risks as to that product candidate.

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 in a timely manner 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.

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 good clinical practices, or 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 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 or applicable non-U.S. regulatory agency may require us to perform additional clinical trials before approving any marketing applications for the relevant jurisdiction. Upon inspection, the FDA or applicable non-U.S. regulatory agency 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

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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.

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.

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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 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 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.

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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.

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 elects to further pursue the development and commercialization of any of the microRNA product candidates that are subject to its strategic alliance agreement with us, or in AstraZeneca's development of RG-125(AZD4076), 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.

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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.

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

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- 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. For example, several new antivirals and antiviral combinations have been approved for the treatment of the Hepatitis C infection since we commenced clinical development of RG-101. Such increased competition may decrease any future potential revenue for RG-101 due to increasing pressure for lower pricing and higher discounts in the commercialization of our product.

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, in order to commercialize RG-101 or to exercise our co-promotion rights with Sanofi with respect to our miR-21 and miR-221/222 programs, we would need to build our sales, marketing, managerial and other non-technical capabilities in order to effectively carry out sales or 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 program 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.

Our current and any future strategic alliance partners 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 existing strategic alliance agreements, Sanofi and AstraZeneca will be responsible for the commercialization of current and any future product candidates developed under their respective programs. If any other product candidates that we 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;

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- 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 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,

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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, 2016 we had 97 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. 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-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

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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 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.

We expect that 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.

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.

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

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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

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 $1.05 to $22.08, through

February 24, 2017. The trading price of our common stock is likely to continue to be volatile.

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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 24, 2017, 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.

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.

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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 will likely be an "emerging growth company" through December 31, 2017, at which time we will lose that status. 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 4,347,250 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.

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

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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, any of which may result in material dilution to investors and/or our existing stockholders. New investors could also be issued securities with rights superior to those of 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 lessor 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 previously adopted an Inducement Plan pursuant to which our management had the ability 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. As of the date of this report, no further awards may be granted under the Inducement Plan; however, 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 increase the number of shares which may be granted under the Inducement Plan, or adopt another inducement plan for which no stockholder approval is required under applicable rules and regulations, and grant options pursuant to such plan, our stockholders may experience additional dilution, which could cause our stock price to fall.

We may be unable to comply with the applicable continued listing requirements of The NASDAQ Global Market.

Our common stock is currently listed on The NASDAQ Global Market, or NASDAQ. In order to maintain this listing, we must satisfy minimum financial and other continued listing requirements and standards, including a minimum closing bid price requirement for our common stock of $1.00 per share. There can be no assurance that we will be able to comply with the applicable listing standards. For example, if we were to fail to meet the minimum bid price requirement for 30 consecutive business days, we could become subject to delisting. Although NASDAQ may provide us with a compliance period in which to regain compliance with the minimum bid price requirement, we cannot assure you that we would be able to regain compliance within the period provided by NASDAQ. In order to regain compliance with such requirement, the closing bid price of our common stock would need to meet or exceed $1.00 per share for at least 10 consecutive business days during the compliance period. If we were not able to regain compliance within the allotted compliance period for this requirement or any other applicable listing standard, including any extensions that may be granted by NASDAQ, our shares of common stock would be subject to delisting. In the event that our common stock is delisted from NASDAQ and is not eligible for quotation or listing on another market or exchange, trading of our common stock could be conducted only in the over-the-counter market or on an electronic bulletin board established for unlisted securities such as the Pink Sheets or the OTC Bulletin Board. In such event, it could become more difficult to dispose of, or obtain accurate price quotations for our common stock and there would likely also be a reduction in our coverage by securities analysts and the news media, which could cause the price of our common stock to decline further.

We are the subject of a putative securities class action lawsuit, and additional securities litigation may be brought against us in the future.

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. On January 31, 2017, a putative class action complaint was filed in the United States District Court for the Southern District of California against us, our Chief Executive Officer, Paul C. Grint, and our Chief Operating Officer, Joseph P. Hagan. The complaint includes claims asserted, on

behalf of certain purchasers of our securities, under Sections 10(b) and 20(a) of the Securities Exchange Act of 1934, as amended. In general, the complaint alleges that between January 21, 2016, and June 27, 2016, the defendants violated the federal securities laws by making materially false and misleading statements regarding our business and the prospects for RG-101, thereby artificially inflating the price of our securities. The plaintiff seeks unspecified monetary damages and other relief. It is possible that additional lawsuits will be filed, or allegations made by stockholders, with respect to these same or other matters and also naming us and/or our officers and directors as defendants. Due to the early stage of these proceedings, we are not able to predict or reasonably estimate the ultimate outcome or possible losses relating to these claims. While we carry liability insurance, there is no assurance that any

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losses we incur in connection with the current lawsuit or any future lawsuits will be covered or that coverage, if any, will be sufficient. In addition, the current lawsuit and similar future litigation 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. In addition, our ability to pay cash dividends is currently prohibited by the terms of our secured debt, and any future debt financing arrangement may contain terms prohibiting or limiting the amount of dividends that may be declared or paid on our common stock. 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:

- 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.

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Item 2. Properties

Our principal corporate facility, which includes administrative offices and a research laboratory, consists of approximately 59,000 square feet of space located in San Diego, California. The term of our lease agreement for this facility expires in April 2024. We also have 7,500 square feet of office and laboratory space located in San Diego, California under a lease agreement that will expire in June 2017. We believe that our existing facilities are adequate for our current needs.

Item 3. Legal Proceedings

On January 31, 2017, a putative class action complaint was filed in the United States District Court for the Southern District of California ("District Court") against us, our Chief Executive Officer, Paul C. Grint, and our Chief Operating Officer, Joseph P. Hagan. The complaint includes claims asserted, on behalf of certain purchasers of our securities, under Sections 10(b) and 20(a) of the Securities Exchange Act of 1934, as amended. In general, the complaint alleges that, between January 21,
2016, and June 27, 2016, the defendants violated the federal securities laws by making materially false and misleading statements regarding our business and the prospects for RG-101, thereby artificially inflating the price of our securities. The plaintiff seeks unspecified monetary damages and other relief. On February 17, 2017, the District Court entered an order stating that defendants need not answer, or otherwise respond, until the District Court enters an order appointing, pursuant to the Private Securities Litigation Reform Act of 1995, lead plaintiff and lead counsel, and the parties then submit a schedule to the District Court for the filing of an amended or consolidated complaint and the timing of defendants' answer or response. We intend to vigorously defend this matter.

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

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, 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
Year Ended December 31, 2016:		
First Quarter	$8.88	$5.14
Second Quarter	$8.90	$2.44
Third Quarter	$4.25	$2.88
Fourth Quarter	$3.65	$2.13

Holders of Record

As of February 24, 2017, there were approximately 9 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. In addition, our ability to pay cash dividends is currently prohibited by the terms of our loan agreement with Oxford.

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, 2016 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 have been included in this Annual Report pursuant to SEC rules and are not intended to forecast or be indicative of possible future performance of our common stock. The graph assumes that all dividends have been reinvested (to date, we have not declared any dividends).

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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, 2016 and 2015 and the related statements of operations for each of the years ended December 31, 2016, 2015 and 2014 and related notes appearing elsewhere in this Annual Report. The balance sheet data as of December 31, 2014, 2013 and 2012 and the statement of operations data for the years ended December 31, 2013 and 2012 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.

	Year ended December 31,				
Statement of operations data	2016	2015	2014	2013	2012
Revenue under strategic alliances and collaborations	$1,194	$20,759	$7,669	$19,569	$12,700
Loss from operations	(81,502)	(54,758)	(44,910)	(17,802)	(12,574)
Net loss	$(81,836)	$(55,748)	$(56,680)	$(18,668)	$(17,408)
Net loss per share, basic and diluted	$(1.55)	$(1.08)	$(1.29)	$(0.49)	$(2.12)

	As of December 31,				
Balance sheet data	2016	2015	2014	2013	2012
Cash, cash equivalents and short-term investments	$76,111	$115,319	*$159,743	$114,005	$98,100
Working capital	73,667	121,626	129,759	106,812	86,161
Total assets	100,661	141,083	171,480	123,065	103,518
Convertible note payable, at fair value	—	—	23,397	11,279	10,134
Accumulated deficit	(273,351)	(191,515)	(135,767)	(79,087)	(60,419)
Total stockholders’ equity	56,075	124,078	132,014	93,457	62,093

*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.”

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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. contributed significant intellectual property, know-how and financial and human capital to pursue the development of drugs targeting microRNAs pursuant to a license and collaboration agreement. microRNAs are naturally occurring ribonucleic acid, or RNA, molecules that play a critical role in regulating key biological pathways. Scientific research has shown that an imbalance, or dysregulation, of microRNAs is directly linked to many diseases. To date, over 500 microRNAs have been identified in humans, each of which bind to multi messenger RNAs (mRNA) that control key aspects of cell biology. Since many diseases are multi-factorial, involving multiple targets and pathways, the ability to modulate multiple pathways 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 modulating the translation of target messenger RNAs. By interacting with many messenger RNAs, a single microRNA can regulate multiple genes involved in 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 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; and
- microRNAs are a relatively new area of biological research for the industry.

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 are using our microRNA expertise to develop chemically modified, single-stranded oligonucleotides that we call anti-miRs to modulate dysregulated microRNAs and return them to their healthy state. We believe microRNAs may play a critical role in complex disease and that targeting them with anti-miRs may become a source of a new and major class of drugs with broad therapeutic application, much like small molecules, biologics and monoclonal antibodies. We have established strategic alliances with AstraZeneca AB and Sanofi to discover, develop and commercialize microRNA therapeutics.

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.

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 of preclinical, clinical, regulatory and commercialization milestones, if at all, the timing and amount

of payments relating to such milestones and the extent to which any of our products are approved and successfully commercialized by us or our strategic alliance partners. If our strategic alliance partners do not elect or otherwise agree to fund our development costs pursuant to our

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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 and the development of our therapeutic programs. 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
- facilities, depreciation and other allocated expenses, which include direct and allocated expenses for rent and maintenance of facilities, depreciation of leasehold improvements and equipment, and laboratory and other supplies.

We expense research and development costs as incurred. We account for nonrefundable advance payments for goods and services that will be used in future research and development activities as expenses when the service has been performed or when the goods have been received. Certain of the raw materials used in the process of manufacturing drug product are capitalized upon their acquisition and expensed upon usage, as we have determined these materials have alternative future use.

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 vast majority of our research and development resources on our lead development programs.

Since our conversion to a corporation in January 2009, we have grown from 15 research and development personnel to 77 and have spent a total of approximately $258.9 million in research and development expenses through December 31, 2016.

The process of conducting clinical trials and preclinical 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 preclinical data, 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. 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 costs will likely include legal fees, Sarbanes-Oxley compliance and other accounting fees and directors' and officers' liability insurance premiums.

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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. Commencing in June 2016, interest expense is primarily attributable to interest charges associated with borrowings under our secured term loan from Oxford. 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 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 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 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, which approximates effort over our estimated period of performance, which for us is typically 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 estimated performance period.

Deferred Revenue

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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 and Preclinical Study Accruals

We make estimates of our accrued expenses for clinical trial and preclinical study activities as of each balance sheet date in our financial statements based on the facts and circumstances known to us at that time. These accruals are based upon 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 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, 2016 and 2015

The following table summarizes our results of operations for the years ended December 31, 2016 and 2015 (in thousands):

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	Years ended December 31,	
	2016	2015
Revenue under strategic alliances and collaborations	$1,194	$20,759
Research and development expenses	64,305	56,387
General and administrative expenses	18,391	19,130
Interest and other expenses	(1,182)	(52)
Loss from changes in valuation of convertible note payable	—	(1,811)

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):

	Years ended December 31,	
	2016	2015
AstraZeneca	$1,122	$18,871
Sanofi	72	71
Biogen	—	1,817
Total revenues under strategic alliances and collaborations	$1,194	$20,759

Revenue under strategic alliances and collaborations was $1.2 million for the year ended December 31, 2016 compared to $20.8 million for the year ended December 31, 2015.

Revenue under the AstraZeneca collaboration and license agreement decreased to $1.1 million for the year ended December 31, 2016 compared to $18.9 million for the year ended December 31, 2015. Revenue recognized in 2016 related to the amortization of upfront payments over our remaining period of performance, which ended in August 2016. In March 2015 and December 2015, we earned milestones of $2.5 million and $10.0 million, respectively, in connection with the preclinical and clinical advancement of RG-125(AZD4076). 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(AZD4076). Revenue of $4.5 million was recognized under the letter agreement for the year ended December 31, 2015. As of December 31, 2015, our obligations under the letter agreement were complete.

Revenue recognized from our agreement with Biogen decreased to zero for the year ended December 31, 2016 compared to $1.8 million for the year ended December 31, 2015. This decrease 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.

As of December 31, 2016, we had $2.1 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

The following table summarizes the components of our research and development expenses for the periods indicated, together with year-over-year changes (dollars in thousands):

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	2016	% of total	2015	% of total	Increase (decrease) $	%
Research and development						
Personnel and internal expenses	$24,452	38 %	$20,629	37 %	$3,823	19 %
Third-party and outsourced expenses	32,430	50 %	26,207	46 %	6,223	24 %
Non-cash stock-based compensation	5,458	8 %	8,075	14 %	(2,617)	(32)%
Depreciation	1,965	4 %	1,476	3 %	489	33 %
Total research and development expenses	$64,305	100%	$56,387	100%	$7,918	

Research and development expenses increased by $7.9 million for the year ended December 31, 2016 compared to the year ended December 31, 2015. The increase was principally driven by a $6.2 million increase in external development expenses, primarily attributable to incremental costs incurred associated with RG-101 Phase II studies, increased costs associated with our global ATHENA natural history of disease study and start-up costs for our RG-012 Phase II study.

General and administrative expenses

General and administrative expenses were $18.4 million for the year ended December 31, 2016 compared to $19.1 million for the year ended December 31, 2015. This change was primarily driven by a decrease in personnel costs, including non-cash stock based compensation, of $0.5 million for the year ended December 31, 2016 compared to the year ended December 31, 2015.

Interest and other expenses

Interest and other expenses were $1.2 million for the year ended December 31, 2016 compared to $0.1 million for the year ended December 31, 2015. This increase was driven by interest expense associated with our outstanding $20.0 million secured term loan from Oxford, which we borrowed in June 2016.

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. 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, 2015 and 2014

The following table summarizes the results of our operations for the periods indicated (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 change in valuation of convertible note payable	(1,811)	(12,118)

Revenue under strategic alliances and collaborations

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. Revenue of $4.5 million was recognized under the January 2015 letter agreement for the year ended December 31, 2015. In March 2015 and December 2015, we earned milestones of $2.5 million and $10.0 million, respectively.

Revenue 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.

Revenue 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.

Revenue 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 research milestone payments under the August 2014 collaboration and license agreement earned in January 2015, May 2015 and September 2015 of $0.1 million, $0.3 million, and $0.3 million, respectively.

Research and development expenses

The following table summarizes the components of our research and development expenses for the periods indicated, together with year-over-year changes (dollars in thousands):

					Increase (decrease)	
	2015	% of total	2014	% of total	$	%
Research and development						
Personnel and internal expenses	$20,629	37 %	$19,617	48 %	$1,012	5 %
Third-party and outsourced expenses	26,207	46 %	16,094	39 %	10,113	63 %
Non-cash stock-based compensation	8,075	14 %	3,939	10 %	4,136	105 %
Depreciation	1,476	3 %	1,396	3 %	80	6 %
Total research and development expenses	$56,387	100 %	$41,046	100 %	$15,341	

Research and development expenses increased by $15.3 million for the year ended December 31, 2015 compared to the year ended December 31, 2014. The increase was principally driven by a $10.1 million increase in third-party and outsourced expenses, primarily attributable to costs incurred associated with the RG-101 Phase II study, preclinical

study costs incurred associated with additional research and development activities and product manufacturing to support the initiation of the RG-125 Phase I clinical study and a $4.1 million increase in non-cash stock-based compensation.

General and administrative expenses

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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 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.

Loss from change in value 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.

LIQUIDITY AND CAPITAL RESOURCES

Since our inception through December 31, 2016, we have received $85.1 million principally from upfront payments, research funding and milestones from our strategic alliances and collaborations, $257.1 million from the sale of our equity and convertible debt securities and $19.8 million in net proceeds from our June 2016 secured term loan from Oxford.

As of December 31, 2016, we had $76.1 million in cash, cash equivalents and short-term investments.

The following table shows a summary of our cash flows for the years ended December 31, 2016, 2015 and 2014 (in thousands):

	Years ended December 31,		
	2016	2015	2014
Net cash (used in) provided by:			
Operating activities	$(56,882)	$(49,859)	$(39,510)
Investing activities	35,311	21,475	(29,207)
Financing activities	20,552	7,017	88,237
Total	$(1,019)	$(21,367)	$19,520

Operating activities

Net cash used in operating activities increased to $56.9 million for the year ended December 31, 2016, compared to $49.9 million and $39.5 million for the years ended December 31, 2015 and December 31, 2014, respectively. Increases in cash used in operating activities were attributable, in part, to net losses of $81.8 million, $55.7 million and $56.7 million for the years ended December 31, 2016, 2015 and 2014, respectively. Adjustments for non-cash charges, including stock-based compensation and changes in value of our convertible note payable, decreased to $16.9 million for the year ended December 31, 2016, compared to $20.3 million and $22.3 million for the years ended December 31, 2015 and 2014, respectively. Changes in working capital resulted in net cash provided by operating activities of $8.1 million for the year ended December 31, 2016 and net cash used in operating activities of $14.5 million and $5.1 million for the years ended December 31, 2015 and 2014, respectively. These changes primarily relate to the timing of cash receipts for upfront payments and milestones.

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 $36.3 million and $22.9 million for the years ended December 31, 2016 and 2015, respectively, compared to net purchases of investments of $28.0 million for the year ended December 31, 2014. Net cash used for purchases of property and equipment was $0.9 million, $1.4 million, and $1.1 million for the years ended December 31, 2016, 2015 and 2014, respectively.

Financing activities

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Net cash provided by financing activities was $20.6 million, $7.0 million and $88.2 million for the years ended December 31, 2016, 2015 and 2014, respectively. In 2016, financing activities included net proceeds from borrowings under a term loan of $19.8 million. 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.

Future Capital Requirements

As of December 31, 2016 we had approximately $76.1 million in cash, cash equivalents and short-term investments. 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;
- 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, 2016 (in thousands):

	Payments due by period				
	Total	2017 <1 year	2018-2019 2-3 years	2020-2021 4-5 years	>5 years
Operating lease obligations relating to facility(1)	$20,000	$2,330	$ 5,230	$ 5,548	$6,892
Outstanding secured term loan	20,000	—	15,000	5,000	—
Annual maintenance fees for license agreements	742	94	188	188	272
Total	$40,742	$2,424	$ 20,418	$ 10,736	$7,164

(1) We lease approximately 59,000 square feet of office and laboratory space in San Diego, California, under an operating lease that expires in April 2024. Additionally, we remain obligated to 7,500 square feet of space under the operating lease for our previous corporate headquarters, which will expire in June 2017. Obligations under all lease agreements are included in the above table.

Off-Balance Sheet Arrangements

As of December 31, 2016, 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

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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 rates were to have occurred on December 31, 2016, this change would not have had a material effect on the fair value of our investment portfolio as of that date.

We also have interest rate exposure as a result of our outstanding $20.0 million secured term loan from Oxford. As of December 31, 2016, the outstanding principal amount of the term loan was $20.0 million. The term loan bears interest at a floating per annum rate equal to (i) 8.51% plus (ii) the greater of (a) the 30 day U.S. Dollar LIBOR rate reported in The Wall Street Journal on the last business day of the month that immediately precedes the month in which the interest will accrue and (b) 0.44%. Changes in the U.S. Dollar LIBOR rate may therefore affect our interest expense associated with the term loan.

If a 10% change in interest rates were to have occurred on December 31, 2016, this change would not have had a material effect on our interest expense 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, 2016 and 2015, 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, 2016. 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, 2016 and 2015, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2016, in conformity with U.S. generally accepted accounting principles.
/s/ Ernst & Young LLP
San Diego, California
March 2, 2017

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Regulus Therapeutics Inc.
BALANCE SHEETS
(in thousands, except share and per share data)

	December 31,	
	2016	2015
Assets		
Current assets:		
Cash and cash equivalents	$14,941	$15,960
Short-term investments	61,170	98,103
Restricted cash	—	1,256
Contract and other receivables	1,657	10,021
Prepaid materials, net	5,552	5,543
Prepaid expenses and other current assets	4,154	3,375
Total current assets	87,474	134,258
Property and equipment, net	11,830	5,400
Intangibles, net	1,015	1,081
Other assets	342	344
Total assets	$100,661	$141,083
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$5,840	$2,717
Accrued liabilities	5,577	6,329
Accrued compensation	2,318	2,392
Current portion of deferred revenue	72	1,194
Total current liabilities	13,807	12,632
Term loan, less debt issuance costs	19,802	—
Deferred revenue, less current portion	1,993	2,065
Deferred rent, less current portion	8,840	2,308
Other long-term liabilities	144	—
Total liabilities	44,586	17,005
Commitments and Contingencies (Note 8)		
Stockholders' equity:		
Common stock, $0.001 par value; 200,000,000 shares authorized, 52,924,805 and 52,669,266 shares issued and outstanding at December 31, 2016 and 2015, respectively	53	53
Additional paid-in capital	329,496	315,673
Accumulated other comprehensive loss	(123)	(133)
Accumulated deficit	(273,351)	(191,515)
Total stockholders' equity	56,075	124,078
Total liabilities and stockholders' equity	$100,661	$141,083

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)

	2016	2015	2014
Revenues:			
Revenue under strategic alliances and collaborations	$ 1,194	$ 20,759	$ 7,669
Total revenues	1,194	20,759	7,669
Operating expenses:			
Research and development	64,305	56,387	41,046
General and administrative	18,391	19,130	11,533
Total operating expenses	82,696	75,517	52,579
Loss from operations	(81,502)	(54,758)	(44,910)
Other income (expense):			
Interest and other income	844	855	388
Interest and other expense	(1,182)	(52)	(39)
Loss from valuation of convertible note payable	—	(1,811)	(12,118)
Loss before income taxes	(81,840)	(55,766)	(56,679)
Income tax benefit (expense)	4	18	(1)
Net loss	$ (81,836)	$ (55,748)	$ (56,680)
Other comprehensive loss:			
Unrealized gain (loss) on short-term investments, net	10	64	(181)
Comprehensive loss	$ (81,826)	$ (55,684)	$ (56,861)
Net loss per share, basic and diluted	$ (1.55)	$ (1.08)	$ (1.29)
Weighted average shares used to compute basic and diluted net loss per share	52,813,474	51,411,353	44,090,165

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, 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	2	6,678	—	—	6,680
Stock-based compensation expense	—	—	15,368	—	—	15,368
Issuance of common stock under Employee Stock Purchase Plan	69,380	—	492	—	—	492
Conversion of convertible note payable into common stock	1,356,738	2	25,206	—	—	25,208
Unrealized gain on short-term investments	—	—	—	64	—	64
Net loss	—	—	—	—	(55,748)	(55,748)
Balance at December 31, 2015	52,669,266	$ 53	$ 315,673	$ (133)	$ (191,515)	$ 124,078
Issuance of common stock upon exercise of options	89,855	—	310	—	—	310
Stock-based compensation expense	—	—	12,872	—	—	12,872
Issuance of common stock under Employee Stock Purchase Plan	165,684	—	641	—	—	641
Unrealized gain on short-term investments	—	—	—	10	—	10
Net loss	—	—	—	—	(81,836)	(81,836)
Balance at December 31, 2016	52,924,805	$ 53	$ 329,496	$ (123)	$ (273,351)	$ 56,075

See accompanying notes to these financial statements.

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Regulus Therapeutics Inc.
STATEMENTS OF CASH FLOWS
(In thousands)

	Years ended December 31,		
	2016	2015	2014
Operating activities			
Net loss	$(81,836)	$(55,748)	$(56,680)
Adjustments to reconcile net loss to net cash used in operating activities			
Depreciation and amortization expense	2,276	1,591	1,490
Loss from valuation of convertible note payable	—	1,811	12,118
Stock-based compensation	12,872	15,368	7,039
Amortization of premium on investments, net	666	1,472	1,597
Other	1,043	98	18
Change in operating assets and liabilities:			
Contracts and other receivables	8,364	(9,746)	(196)
Prepaid materials	(616)	(3,460)	(641)
Prepaid expenses and other assets	(778)	(683)	(1,241)
Accounts payable	3,123	529	940
Accrued liabilities	(871)	2,094	556
Accrued compensation	(74)	284	811
Deferred revenue	(1,194)	(3,090)	(5,039)
Deferred rent and other liabilities	143	(379)	(282)
Net cash used in operating activities	(56,882)	(49,859)	(39,510)
Investing activities			
Purchases of short-term investments	(65,110)	(78,401)	(113,417)
Sales and maturities of short-term investments	101,387	101,306	85,421
Purchases of property and equipment	(913)	(1,363)	(1,146)
Acquisition of intangibles	(53)	(67)	(65)
Net cash provided by (used in) investing activities	35,311	21,475	(29,207)
Financing activities			
Proceeds from borrowing under term loan, net	19,768	—	—
Proceeds from issuance of common stock, net	641	492	86,146
Proceeds from exercise of common stock options	310	6,680	2,233
Principal payments on other long-term obligations	(167)	(155)	(142)
Net cash provided by financing activities	20,552	7,017	88,237
Net (decrease) increase in cash and cash equivalents	(1,019)	(21,367)	19,520
Cash and cash equivalents at beginning of period	15,960	37,327	17,807
Cash and cash equivalents at end of period	$14,941	$15,960	$37,327
Supplemental disclosure of cash flow information			
Net changes in restricted cash	$(1,256)	$1,256	$—
Interest paid	$(981)	$(27)	$(39)
Income taxes paid	$(1)	$(1)	$(1)
Supplemental disclosure of non-cash investing and financing activities			
Allowance for tenant improvements	$6,653	$1,656	$—
Amounts accrued for property and equipment	$292	$223	$76
Amounts accrued for patent expenditures	$—	$28	$42

See accompanying notes to these financial statements.

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Regulus Therapeutics Inc.
NOTES TO FINANCIAL STATEMENTS
1. The Business, Basis of Presentation and Summary of Significant Accounting Policies

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., 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. Regulus Therapeutics Inc. was converted to a Delaware corporation on January 2, 2009. As used in this report, unless the context suggests otherwise, “the Company,” “our,” “us” and “we” means Regulus Therapeutics Inc.

Use of Estimates

Our financial statements are prepared in accordance with United States Generally Accepted Accounting Principles, which requires us to make estimates and assumptions that affect the reported amounts of assets, liabilities, revenues and expenses and the disclosure of contingent assets and liabilities in our financial statements and accompanying notes. An estimated loss contingency is accrued in our financial statements if it is probable that a liability has been incurred and the amount of the loss can be reasonably estimated. Although these estimates are based on our knowledge of current events and actions we may undertake in the future, actual results may ultimately differ from these estimates and assumptions.

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 AB (“AstraZeneca”), 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, which approximates effort over our estimated period of performance, which for us is typically 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 estimated performance period.

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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.

Stock-Based Compensation

We account for stock-based compensation expense related to stock options granted to employees and members of our board of directors by estimating the fair value of each stock option on the date of grant using the Black-Scholes option pricing model. We recognize stock-based compensation expense using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), we recognize compensation expense over the requisite service period for each separately vesting tranche of the award as though the award was in substance multiple awards, resulting in accelerated expense recognition over the vesting period. For performance-based awards granted to employees (i) the fair value of the award is determined on the grant date, (ii) we assess the probability of the individual milestones under the award being achieved and (iii) the fair value of the shares subject to the milestone is expensed over the implicit service period commencing once management believes the performance criteria is probable of being met.

We account for stock options granted to non-employees using the fair value approach. Stock options granted to non-employees are subject to periodic revaluation over their vesting terms.

Prepaid Materials

We capitalize the purchase of certain raw materials and related supplies for use in the manufacturing of drug product in our clinical development programs, as we have determined that these materials have alternative future use. We can use these raw materials and related supplies in multiple clinical drug products, and therefore have future use independent of the development status of any particular drug program until it is utilized in the manufacturing process. We periodically review these capitalized materials for indicators of impairment, including shelf life, continued alternative future use and obsolescence. As of December 31, 2016 and 2015, our prepaid materials balance was $5.6 million, net of a $0.6 million reserve, and $5.5 million, respectively.

Research and Development

Research and development costs are expensed as incurred and consist of costs associated with research activities supporting our drug discovery efforts, compensation and related benefits, non-cash stock-based compensation, license fees, laboratory supplies and associated overhead and facility costs.

Income Taxes

Income taxes are accounted for under the asset and liability method. This approach requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of the differences between the tax basis of assets or liabilities and their carrying amounts in the financial statements using the enacted tax rates and laws that are anticipated to be in effect when the differences are expected to reverse. We provide a valuation allowance against net deferred tax assets if it is more likely than not that these items will either expire before the Company is able to realize their benefit or if future deductibility is uncertain.

In accordance with the accounting standards for uncertain tax positions, the Company evaluates the recognition threshold and measurement attribute criteria for the financial statement recognition and measurement of tax positions taken or expected to be taken in a tax return. For those benefits to be recognized, a tax position must be more likely than not to be sustained upon examination by taxing authorities.

Fair Value Option

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 (see Note 9).

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Clinical Trial and Preclinical Study Accruals

We make estimates of our accrued expenses for clinical trial and preclinical study activities as of each balance sheet date in our financial statements based on the facts and circumstances known to us at that time. These accruals are based upon 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 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.

Cash and Cash Equivalents

We classify time deposits and other investments that are highly liquid and have maturities of 90 days or less at the date of purchase as cash equivalents. The carrying amounts approximate fair value due to the short maturities of these instruments.

Restricted Cash

Restricted cash consists of amounts received for a specific and limited purpose, and therefore not available for general operating activities. In August 2015, we received $1.4 million in connection with our facility lease agreement with Walton Torrey Owner B, L.L.C, entered into in July 2015. The use of these funds were restricted to costs associated with the relocation of our corporate headquarters. As of December 31, 2016, our restricted cash balance was zero.

Short-Term Investments

We carry short-term investments classified as available-for-sale at fair value as determined by prices for identical or similar securities at the balance sheet date. Our short-term investments consist of both Level 1 and Level 2 financial instruments in the fair value hierarchy. We record unrealized gains and losses as a component of other comprehensive loss within the statements of operations and comprehensive loss and as a separate component of stockholders' equity. We determine the realized gains or losses of available-for-sale securities using the specific identification method and include net realized gains and losses in interest income.

At each balance sheet date, we assess available-for-sale securities in an unrealized loss position to determine whether the unrealized loss is other-than-temporary. We consider factors including: the significance of the decline in value compared to the cost basis, underlying factors contributing to a decline in the prices of securities in a single asset class, the length of time the market value of the security has been less than its cost basis, the security's relative performance versus its peers, sector or asset class, expected market volatility and the market and economy in general. When we determine that a decline in the fair value below its cost basis is other-than-temporary, we recognize an impairment loss in the year in which the other-than-temporary decline occurred. We determined that there were no other-than-temporary declines in the value of short-term investments as of December 31, 2016 or 2015.

Concentrations of Credit Risk

Financial instruments that potentially subject us to significant concentrations of credit risk consist primarily of cash equivalents and short-term investments. We maintain deposits in federally insured financial institutions in excess of federally insured limits. We have not experienced any material losses in such accounts and believe we are not exposed to significant risk. We maintain our cash equivalents and short-term investments with two highly accredited financial institutions. We invest our excess cash primarily in commercial paper, certificates of deposit and debt instruments of financial institutions and corporations, United States Treasury securities and United States government-sponsored enterprise securities. Additionally, we adhere to established guidelines regarding approved investments and maturities

of investments, which are designed to preserve their principal value and maintain liquidity.

Property and Equipment

We carry our property and equipment at cost, which consists of lab equipment, computer equipment and software, furniture and fixtures and leasehold improvements. Property and equipment is depreciated using the straight-line method over the estimated useful lives (generally three to five years). Leasehold improvements are amortized over the lesser of their useful

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life or the remaining lease term, including any renewal periods that are deemed to be reasonably assured. Repair and maintenance costs that do not improve service potential or extend economic life are expensed as incurred.

Intangibles

We capitalize costs which consist principally of outside legal costs and filing fees related to obtaining patents. We review our capitalized patent costs periodically to determine that they include costs for patent applications that have future value and an alternative future use. We evaluate costs related to patents that we are not actively pursuing and write off these costs. We amortize patent costs over their patent lives, beginning with the date the patents are issued. The weighted average remaining life of the issued patents was approximately 10 years at December 31, 2016.

We obtain licenses from third parties and capitalize the costs related to exclusive licenses that have alternative future use within multiple potential programs. We amortize capitalized licenses over their estimated useful life or term of the agreement, which for current licenses is 10 years.

Impairment of Long-Lived Assets

We regularly review the carrying amount of our property, equipment and intangible assets to determine whether indicators of impairment may exist which warrant adjustments to carrying values or estimated useful lives. If indications of impairment exist, projected future undiscounted cash flows associated with the asset are compared to the carrying amount to determine whether the asset's value is recoverable. If the carrying value of the asset exceeds such projected undiscounted cash flows, the asset will be written down to its estimated fair value. No impairment charges were recorded during the years ended December 31, 2016, 2015 or 2014.

Segment Reporting

Operating segments are identified as components of an enterprise about which separate discrete financial information is available for evaluation by the chief operating decision-maker in making decisions regarding resource allocation and assessing performance. To date, we have viewed our operations and managed our business as one segment operating primarily within the United States.

Comprehensive Loss

Comprehensive loss is defined as the change in equity during a period from transactions and other events and/or circumstances from non-owner sources. Our only component of other comprehensive loss is unrealized gains (losses) on available-for-sale securities. Comprehensive gains (losses) have been reflected in the statements of operations and comprehensive loss and as a separate component in the statements of stockholders' equity for all periods presented.

Recent Accounting Pronouncements

In May 2014, the Financial Accounting Standards Board, or FASB, issued Accounting Standards Update, or ASU, No. 2014-09, Revenue from Contracts with Customers (Topic 606), which outlines a single comprehensive model for entities to use in accounting for revenue arising from contracts with customers and supersedes most current revenue recognition guidance, including industry-specific guidance. ASU 2014-09 outlines a five-step process for revenue recognition that focuses on transfer of control, as opposed to transfer of risk and rewards, and also requires enhanced disclosures regarding the nature, amount, timing and uncertainty of revenues and cash flows from contracts with customers. Major provisions include determining which goods and services are distinct and require separate accounting (performance obligations), how variable consideration (which may include change orders and claims) is recognized, whether revenue should be recognized at a point in time or over time and ensuring the time value of money is considered in the transaction price.

The FASB issued supplemental adoption guidance and clarification to ASU 2014-09 in March 2016, April 2016 and May 2016 within ASU 2016-08, Revenue from Contracts with Customers: Principal vs. Agent Considerations, ASU 2016-10, Revenue from Contracts with Customers: Identifying Performance Obligations and Licensing and ASU 2016-12, Revenue from Contracts with Customers: Narrow-Scope Improvements and Practical Expedients, respectively. ASU 2014-09 and the related supplemental ASUs are effective for fiscal years beginning after December 15, 2017 and interim periods therein. The ASU permits two methods of adoption: the full retrospective method or the modified retrospective method. We currently plan on applying the modified retrospective method upon adoption in the first quarter of 2018, and currently do not anticipate that the adoption of this ASU will have a material impact with

regard to our current contracts.

In August 2014, the FASB issued ASU No. 2014-15, Presentation of Financial Statements Going Concern, which requires management to assess an entity's ability to continue as a going concern, and to provide related footnote disclosure in

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certain circumstances. This standard is effective for annual reporting periods ending after December 15, 2016 and interim periods thereafter. The adoption of this guidance had no impact on our financial statements.

In April 2015, the FASB issued ASU No. 2015-03, Interest- Imputation of Interest: Simplifying the Presentation of Debt Issuance Costs, which requires that debt issuance costs related to a recognized debt liability be presented in the balance sheet as a direct deduction from the carrying amount of that debt liability, consistent with debt discounts. The recognition and measurement guidance for debt issuance costs were not affected by the amendments in ASU No. 2015-03. In June 2016, upon entering into a loan and security agreement, we adopted ASU No. 2015-03, which resulted in the classification of $0.2 million of debt issuance costs against the principal balance of our outstanding term loan of $20.0 million.

In January 2016, the FASB issued ASU No. 2016-01, Recognition and Measurement of Financial Assets and Financial Liabilities, which eliminates the requirement for public companies to disclose the method(s) and significant assumptions used to estimate the fair value that is required to be disclosed for financial instruments measured at amortized cost on the balance sheet. Additionally, the standard requires public companies to use the exit price notion when measuring the fair value of financial instruments for disclosure purposes. Furthermore, the standard requires presentation of financial assets and liabilities by measurement category and form of financial asset on the balance sheet or accompanying notes to the financial statements. The standard is effective for annual reporting periods beginning after December 15, 2017, including interim periods within those annual reporting periods. Early application is permitted. The adoption of this guidance will have no impact on our financial statements.

In February 2016, the FASB issued ASU No. 2016-02, Leases, which increases transparency and comparability among organizations by requiring recognition of lease assets and lease liabilities on the balance sheet and disclosure of key information about leasing arrangements. The standard is effective for annual reporting periods beginning after December 15, 2018, including interim periods within those annual reporting periods. Early application is permitted. We are currently evaluating the impact of adoption on our financial statements.

In March 2016, the FASB issued ASU No. 2016-09, Compensation - Stock Compensation: Improvements to Employee Share-Based Payment Accounting, which is intended to simplify several aspects of accounting for share-based payment transactions, including the income tax consequences, classification of awards as either equity or liabilities, and classification on the statement of cash flows. The standard is effective for annual reporting periods beginning after December 15, 2016, and interim periods within those annual reporting periods. Early application is permitted. We intend to adopt this guidance in the first quarter of 2017. We expect that the adoption of this guidance will increase our deferred tax assets with a corresponding increase to our valuation allowance. We maintained a full valuation allowance against our deferred tax assets at December 31, 2016.

In August 2016, the FASB issued ASU No. 2016-15, Statement of Cash Flows: Classification of Certain Cash Receipts and Cash Payments, which addresses the presentation and classification of certain cash receipts and cash payments in the statement of cash flows under Accounting Standards Codification 230. The standard is effective for annual reporting periods beginning after December 15, 2017, and interim periods within those annual reporting periods. Early application is permitted. The adoption of this guidance will have no impact on our financial statements.

In November 2016, the FASB issued ASU No. 2016-18, Statement of Cash Flows: Restricted Cash, which requires restricted cash and restricted cash equivalents to be included with cash and cash equivalents when reconciling the beginning-of-period and end-of-period total amounts shown on the statement of cash flows. The standard is effective for annual reporting periods beginning after December 15, 2017, and interim periods within those annual reporting periods. Early application is permitted. We have not elected to early adopt this standard as of December 31, 2016. Upon adoption, the 2016 period in our three-year statements of cash flows will include $1.3 million of restricted cash in cash and cash equivalents at the beginning of the period. We do not expect any additional impact on our financial statements.

2. Net Loss Per Share

Basic net loss per share is calculated by dividing the net loss by the weighted average number of common shares outstanding for the period, without consideration for common stock equivalents. Diluted net loss per share is calculated by dividing the net loss by the weighted-average number of common share equivalents outstanding for the period determined using the treasury-stock method. Dilutive common stock equivalents are comprised of options

outstanding under our stock option plans and convertible note payable, which was converted into common stock in January 2015. For all periods presented, there is no difference in the number of shares used to calculate basic and diluted net loss per share.

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Potentially dilutive securities not included in the calculation of diluted net loss per share because to do so would be anti-dilutive are as follows (in common equivalent shares):

	Years ended December 31,		
	2016	2015	2014
Common stock options	5,553,210	1,674,119	2,566,423
Convertible note payable	—	—	1,461,474
Total	5,553,210	1,674,119	4,027,897

3. Investments

We invest our excess cash in commercial paper and debt instruments of financial institutions and corporations, United States Treasury securities and United States government-sponsored enterprise securities. As of December 31, 2016, our short-term investments had a weighted average maturity of less than two years.

The following tables summarize our short-term investments (in thousands):

	Maturity (in years)	Amortized cost	Unrealized Gains	Losses	Estimated fair value
As of December 31, 2016					
Corporate debt securities	2 or less	$ 49,185	$ 12	$ (77)	$ 49,120
Certificates of deposit	1 or less	9,291	—	—	9,291
Commercial paper	1 or less	1,247	—	—	1,247
U.S. treasury securities	1 or less	1,001	—	(1)	1,000
Debt securities of U.S. government-sponsored agencies	1 or less	512	—	—	512
Total		$ 61,236	$ 12	$ (78)	$ 61,170

	Maturity (in years)	Amortized cost	Unrealized Gains	Losses	Estimated fair value
As of December 31, 2015					
Corporate debt securities	2 or less	$ 81,054	$ 16	$ (103)	$ 80,967
Certificates of deposit	2 or less	13,640	—	—	13,640
Commercial paper	1 or less	3,490	6	—	3,496
Total		$ 98,184	$ 22	$ (103)	$ 98,103

4. Fair Value Measurements

We have certain financial assets and liabilities recorded at fair value which have been classified as Level 1, 2, or 3 within the fair value hierarchy as described in the accounting standards for fair value measurements.

Accounting standards define fair value as the exchange price that would be received for an asset or paid to transfer a liability (an exit price) in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants as of the measurement date. Market participants are buyers and sellers in the principal market that are (i) independent, (ii) knowledgeable, (iii) able to transact, and (iv) willing to transact. The accounting standards provide an established hierarchy for inputs used in measuring fair value that maximizes the use of observable inputs and minimizes the use of unobservable inputs by requiring that the most observable inputs be used when available. Observable inputs are inputs that market participants would use in valuing the asset or liability and are developed based on market data obtained from independent sources. Unobservable inputs are inputs that reflect our assumptions about the factors that market participants would use in valuing the asset or liability. The accounting standards prioritize the inputs used in measuring the fair value into the following hierarchy:

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- 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 within Level 1 that are observable for the instrument such as quoted prices for similar instruments in active markets, quoted prices for identical or similar instruments in markets with insufficient volume or infrequent transactions (less active markets) or model-driven valuations in which significant inputs are observable or can be derived principally from, or corroborated by, observable market data.
- Level 3 includes financial instruments for which fair value is derived from valuation techniques in which one or more significant inputs are unobservable, including management's own assumptions.

The following table presents our fair value hierarchy for assets and liabilities measured at fair value on a recurring basis as of December 31, 2016 and December 31, 2015 (in thousands):

	Fair value as of December 31, 2016			
	Total	Level 1	Level 2	Level 3
Assets:				
Cash equivalents	$13,578	$13,578	$—	$ —
Corporate debt securities	49,120	—	49,120	—
Certificates of deposit	9,291	—	9,291	—
Commercial paper	1,247	—	1,247	—
U.S. treasury securities	1,000	—	1,000	—
Debt securities of U.S. government-sponsored agencies	512	—	512	—
	$74,748	$13,578	$61,170	$ —

	Fair value as of December 31, 2015			
	Total	Level 1	Level 2	Level 3
Assets:				
Cash equivalents	$15,152	$15,152	$—	$ —
Corporate debt securities	80,967	—	80,967	—
Certificates of deposit	13,640	—	13,640	—
Commercial paper	3,496	—	3,496	—
	$113,255	$15,152	$98,103	$ —

We obtain pricing information from quoted market prices or quotes from brokers/dealers. We generally determine the fair value of our investment securities using standard observable inputs, including reported trades, broker/dealer quotes, bids and/or offers. Refer to Note 3 for information regarding our investments.

5. Strategic Alliances and Collaborations

The following table summarizes our total revenues from our strategic alliances and collaborations during the periods presented (in thousands):

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	Year ended December 31,		
	2016	2015	2014
AstraZeneca	$1,122	$18,871	$1,859
Sanofi	72	71	979
GSK	—	—	3,509
Biogen	—	1,817	1,122
Other	—	—	200
Total	$1,194	$20,759	$7,669

AstraZeneca

In August 2012, we entered into a collaboration and license agreement with AstraZeneca. Under the terms of the agreement, we agreed to collaborate with AstraZeneca to identify, research and develop compounds targeting three microRNA alliance targets primarily in the fields of cardiovascular diseases, metabolic diseases and oncology. Pursuant to the agreement, we granted AstraZeneca an exclusive, worldwide license to develop, manufacture and commercialize lead compounds designated by AstraZeneca in the course of the collaboration activities against the alliance targets for all human therapeutic uses. Under the terms of the agreement we were required to use commercially reasonable efforts to perform all research, development and manufacturing activities described in the research plan, at our cost, until the acceptance of an investigational new drug application ("IND") or the end of the research term, which expired in August 2016.

Under the terms of the agreement, we received an upfront payment of $3.0 million in October 2012. We determined the elements within the agreement should be treated as a single unit of accounting because the delivered element, the license, did not have stand-alone value. As a result, we recognized revenue related to the upfront payment on a straight-line basis over the period of performance, which was four years based on the term of the research and development plan which ended in August 2016.

In connection with the collaboration and license agreement and concurrently with our initial public offering, we sold AstraZeneca 6,250,000 shares of our common stock in a private placement at a price per share of $4.00. Under the terms of the Common Stock Purchase Agreement ("CSPA"), AstraZeneca could not sell, transfer, make any short sale of, or grant any option for the sale of any common stock for a 365-day period following the effective date of our initial public offering. The CSPA and collaboration and license agreement were negotiated concurrently and were therefore evaluated as a single agreement. Based upon restricted stock studies of similar duration and a Black-Scholes valuation to measure a discount for lack of marketability, $4.3 million was attributed to the collaboration and license agreement. We recognized the $4.3 million into revenue ratably over the period of performance of the collaboration of four years, which ended in August 2016.

In March 2015, we earned a $2.5 million preclinical milestone payment upon AstraZeneca’s selection of RG-125(AZD4076), a GalNAc-conjugated anti-miR targeting microRNA-103/107, as a lead compound under the agreement. 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(AZD4076). If RG-125(AZD4076) is successfully developed and commercialized through pre-agreed sales targets, we could receive additional milestone payments of up to $160.0 million, including up to $32.5 million for clinical milestones, and up to $127.5 million for commercialization milestones. In addition, we are entitled to receive royalties based on a percentage of net sales which will range from the mid to high single digits, depending upon the volume of sales, which royalties may be reduced in certain, limited circumstances.

We evaluated the contingent event-based payments under our collaboration and license agreement with AstraZeneca and determined that the preclinical milestone and the milestone earned for the initiation of a Phase I clinical trial met the definition of substantive milestones. Accordingly, revenue for these achievements was recognized in its entirety in the period when the milestone was achieved and collectability was reasonably assured. Other contingent event-based payments under the agreement for which payment is contingent upon the results of AstraZeneca’s performance will not be accounted for using the milestone method. Such payments will be recognized as revenue over the remaining estimated period of performance, if any, and when collectability is reasonably assured.

In January 2015, we entered into a letter agreement with AstraZeneca to amend the collaboration and license agreement. Under the terms of the letter agreement, we agreed to perform additional miR-103/107 program research and development activities related to RG-125(AZD4076). AstraZeneca agreed to fund 50% of the costs for these additional activities, as outlined in the letter agreement. In accordance with the collaboration and license agreement, AstraZeneca funded 100% of the costs for product manufacturing activities outlined in the letter agreement necessary to support a Phase I clinical study. In December

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2015, we completed a technology transfer to AstraZeneca and have no further obligations to AstraZeneca for future development of RG-125(AZD4076). We recognized $4.5 million for the year ended December 31, 2015 for the performance of research and development and product manufacturing activities outlined in the letter agreement. As of December 31, 2015, our obligations under the letter agreement were complete.

Sanofi

In July 2012, we amended and restated our collaboration and license agreement with Sanofi to expand the potential therapeutic applications of the microRNA alliance targets to be developed under such agreement. We determined that the elements within the strategic alliance agreement with Sanofi should be treated as a single unit of accounting because the delivered elements did not have stand-alone value to Sanofi. The following elements were delivered as part of the strategic alliance with Sanofi: (1) a license for up to four microRNA targets; and (2) a research license under our technology alliance.

In June 2013, the original research term expired, upon which we and Sanofi entered into an option agreement pursuant to which Sanofi was granted an exclusive right to negotiate the co-development and commercialization of certain of our unencumbered microRNA programs and we were granted the exclusive right to negotiate with Sanofi for co-development and commercialization of certain miR-21 anti-miRs in oncology and Alport syndrome. 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 under any future co-development and commercialization agreement we enter pursuant to the option agreement. Revenue associated with the creditable portion of this option payment remained deferred as of December 31, 2016, and will remain 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 in January 2014.

In February 2014, we and Sanofi entered into a second amended and restated collaboration and license agreement (the "2014 Sanofi Amendment") to renew our strategic alliance to discover, develop and commercialize microRNA therapeutics to focus on specific orphan disease and oncology targets. Under the terms of our renewed alliance, Sanofi will have opt-in rights to our clinical fibrosis program targeting miR-21 for the treatment of Alport syndrome, our preclinical program targeting miR-21 for oncology indications, and our preclinical program targeting miR-221/222 for hepatocellular carcinoma ("HCC"). We are responsible for developing each of these programs to proof-of-concept, at which time Sanofi has an exclusive option on each program. 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. We are eligible to receive royalties on microRNA therapeutic products commercialized by Sanofi and will have the right to co-promote these products.

In connection with the 2014 Sanofi Amendment, we entered into a Common Stock Purchase Agreement (the "Purchase Agreement"), pursuant to which we sold 1,303,780 shares of our common stock to Aventisub LLC (formerly Aventis Holdings, Inc.) ("Aventis"), an entity affiliated with Sanofi, in a private placement at a price per share of $7.67 for an aggregate purchase price of $10.0 million. Under the terms of the Purchase Agreement, Aventis was not permitted to sell, transfer, make any short sale of, or grant any option for the sale of any common stock for the 12-month period following its effective date. The Purchase Agreement and the 2014 Sanofi Amendment were negotiated concurrently and were therefore evaluated as a single agreement. Based upon restricted stock studies of similar duration and a Black-Scholes valuation to measure the discount for lack of marketability, approximately $0.4 million of the proceeds from the Purchase Agreement was attributed to the 2014 Sanofi Amendment, and represents consideration for the value of the program targeting miR-221/222 for HCC. As this element does not have stand-alone value, we are recognizing the $0.4 million allocated consideration into revenue ratably over the estimated period of performance of the miR-221/222 program. As of December 31, 2016, deferred revenue associated with the Purchase Agreement and the 2014 Sanofi Amendment was $0.2 million, which we are expecting to recognize over the remaining estimated period of performance of approximately three years.

We are eligible to receive milestone payments of up to $101.8 million for proof-of-concept option exercise fees (net of $1.25 million creditable, as noted above), $15.0 million for clinical milestones and up to $300.0 million for regulatory and commercial milestones. In addition, we are entitled to receive royalties based on a percentage of net sales of any products from the miR-21 and miR-221/222 programs which, in the case of sales in the United States, will be in the middle of the 10 to 20% range, and, in the case of sales outside of the United States, will range from the low end to the middle of the 10 to 20% range, depending upon the volume of sales. If we exercise our option to co-promote a product, we will continue to be eligible to receive royalties on net sales of each product in the United States at the same rate, unless we elect to share a portion of Sanofi's profits from sales of such product in the United States in lieu of royalties.

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We have evaluated the contingent event-based payments under the 2014 Sanofi Amendment and determined that the milestone payments meet the definition of substantive milestones. Accordingly, revenue for these achievements will be recognized in their entirety in the period when the milestone is achieved and collectability is reasonably assured. Other contingent event-based payments under the 2014 Sanofi Amendment for which payment is contingent upon the results of Sanofi's performance will not be accounted for using the milestone method. Such payments will be recognized as revenue over the remaining estimated period of performance, if any, and when collectability is reasonably assured.

Biogen

In August 2014, we entered into a collaboration and license agreement with Biogen to collaborate on microRNA biomarkers for multiple sclerosis. Pursuant to the terms of the collaboration and license agreement, we received an upfront payment of $2.0 million, which was treated as a single unit of accounting as the license did not have stand-alone value. The $2.0 million up-front payment was recognized on a straight-line basis over the estimated period of performance of approximately one year, ending September 2015.

In July 2015, the collaboration and license agreement was amended to modify the conditions of the third research-based milestone. Additionally, the amendment extended the expected research term from 12 months to 14 months. We recognized the remaining upfront payment on a straight-line basis over the amended expected term. As of December 31, 2015, our period of performance was complete and the deferred revenue balance was zero.

In January 2015, May 2015, and September 2015, we earned research milestone payments under the collaboration and license agreement of $0.1 million, $0.3 million and $0.3 million, respectively. These milestone payments met the definition of substantive milestones and, accordingly, revenue for these achievements was recognized in the period the milestones were achieved and collectability was reasonably assured.

6. Property and Equipment, net

The following table summarizes our major classes of property and equipment (in thousands):

	December 31,	
	2016	2015
Laboratory equipment	$7,932	$7,310
Computer equipment and software	265	305
Furniture and fixtures	706	138
Leasehold improvements	10,469	1,930
Construction in progress	261	2,167
	19,633	11,850
Less accumulated depreciation and amortization	(7,803)	(6,450)
Property and equipment, net	$11,830	$5,400

Depreciation and amortization of property and equipment of $2.2 million, $1.5 million and $1.4 million was recorded for the years ended December 31, 2016, 2015 and 2014, respectively.

7. Intangible Assets, net

The following table summarizes our major classes of intangible assets (in thousands):

	December 31,	
	2016	2015
Patents	$1,102	$1,081
Licenses	379	379
	1,481	1,460
Accumulated amortization	(466)	(379)
Intangibles, net	$1,015	$1,081

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Intangible asset amortization of $0.1 million was recorded for each of the years ended December 31, 2016, 2015 and 2014, respectively. Amortization of these intangible assets over the next five years is expected to be approximately $0.1 million per year.

8. Commitments and Contingencies

Operating Lease

In July 2015, we entered into a new operating lease agreement (the "Lease") for office and laboratory space in San Diego, California, for a term of 96 months from the lease commencement date, and moved the Company's headquarters into this new space in May 2016. In conjunction with the Lease, we received $1.4 million from our landlord in August 2015 for assistance with costs associated with the relocation of our corporate headquarters. These funds were received for a specific and limited purpose, and therefore were classified as restricted cash and tenant incentive obligation on the Company's balance sheet. The restricted cash balance was zero and $1.3 million as of December 31, 2016 and 2015, respectively. In addition, the Lease provided a tenant improvement allowance of up to $8.5 million, which was to be used for non-structural leasehold improvements at the new facility. The improvements at the new facility were complete in the second half of 2016, with approximately $8.2 million of the allowance having been used. Under the lease, any unused tenant improvement allowance up to $0.4 million could be used to offset future cash rent. The $0.3 million unused tenant improvement allowance was applied as a credit against future rent payments. The $1.4 million tenant incentive and $8.2 million tenant improvement allowance were classified as deferred rent on the Company's balance sheet and are amortized against rent expense on a straight-line basis over the term of the lease, which commenced upon lease inception.

Previous to moving into our new Company headquarters in May 2016, the Company leased separate office and laboratory space in San Diego, California for use as the Company's corporate headquarters and research facility under an operating lease agreement ("Prior Lease"). The Prior Lease commenced in July 2010 and expires in June 2017. The Prior Lease was amended in November 2012 to increase rented space ("the Additional Space"). Early termination rights were provided with respect to a portion of the space under the Prior Lease after the 60th month of the lease, on condition of at least 9 months prior written notice. No early termination rights were available for the Additional Space.

In October 2015, we provided written notice to our landlord of our election to early terminate the Prior Lease. The effective date of termination of the Prior Lease was June 30, 2016. Termination fees associated with the early termination of the Lease were not material. The Additional Space occupied in conjunction with the amendment of the Prior Lease in November 2012 expires in June 2017. The Additional Space was sublet by the Company in August 2016 for a period extending through the June 2017 expiration of the Prior Lease term. Future sublease income of $0.2 million will be received through the expiration of this sublease agreement in June 2017.

Rent expense for the years ended December 31, 2016, 2015 and 2014 was approximately $1.2 million, $0.6 million and $0.7 million, respectively. We account for the difference between the minimum lease payments and the straight-line amount as deferred rent. Deferred rent under the Lease, which is included in other long-term liabilities, was approximately $10.1 million and zero at December 31, 2016 and 2015, respectively. Deferred rent under the Prior Lease was zero and $0.4 million at December 31, 2016 and 2015, respectively. In connection with the exit and subsequent sublet of the Additional Space, we recorded a liability, which is included in other current liabilities, for unused office space beginning August 2016. As of December 31, 2016, unused office liability was approximately $0.2 million and will amortize against rent expense through the expiration of the Prior Lease term in June 2017. We also pay property taxes, maintenance and insurance, which are expensed as incurred.

The future minimum payment summary below includes amounts payable over the remaining period of the Lease and the Prior Lease.

As of December 31, 2016, aggregate future annual minimum lease payments for our operating leases are as follows (in thousands):

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2017	$2,330
2018	2,576
2019	2,654
2020	2,733
2021	2,815
Thereafter	6,892
	$20,000

License Agreements

We have license agreements with third parties that require us to make annual license maintenance payments and future payments upon the success of licensed products that include milestones and/or royalties. Minimum future payments over the next five years are not material.

9. Convertible Note Payable

In October 2012, in conjunction with our initial public offering the Post-IPO GSK Note was established in the principal amount of $5.4 million, with a maturity date of October 9, 2015. On January 29, 2015, the principal amount outstanding under the Post-IPO GSK Note of $5.4 million was converted into 1,356,738 shares of our common stock at a conversion price of $4.00 per share. We recorded a loss from the change in valuation of the convertible note payable of zero, $1.8 million and $12.1 million on the statements of operations and comprehensive loss for the years ended December 31, 2016, 2015 and 2014, respectively.

10. Term Loan

On June 17, 2016, we entered into a loan and security agreement ("Loan Agreement") with Oxford Finance, LLC, ("Oxford"), pursuant to which Oxford agreed to lend us up to $30.0 million, issuable in two separate term loans of $20.0 million (the "Term A Loan") and $10.0 million (the "Term B Loan"). We collectively refer to the Term A Loan and the Term B Loan as Term Loans. On June 22, 2016, we received $20.0 million in proceeds from the Term A Loan, net of debt issuance costs. Under the terms of the Loan Agreement we may, at our sole discretion, borrow $10.0 million under the Term B Loan following the achievement of a defined milestone event until the earlier of 60 days thereafter or March 31, 2017.

All outstanding Term Loans will mature on June 1, 2020 (the “Maturity Date”) and we will have interest-only payments through June 1, 2018, followed by 24 equal monthly payments of principal and unpaid accrued interest. The Term Loans will bear interest at a floating per annum rate equal to (i) 8.51% plus (ii) the greater of (a) the 30 day U.S. Dollar LIBOR rate reported in The Wall Street Journal on the last business day of the month that immediately precedes the month in which the interest will accrue and (b) 0.44%.

We have the option to prepay all, but not less than all, of the borrowed amounts, provided that we will be obligated to pay a prepayment fee equal to (i) 2% of the outstanding principal balance of the applicable Term Loan if prepayment is made prior to the second anniversary of the applicable funding date of the Term Loan, provided no prepayment fee will be due in connection with a prepayment made on or prior to the first anniversary of the applicable funding date of the Term Loan in connection with an acquisition of our company, or (ii) 1% of the applicable Term Loan prepaid thereafter and prior to the Maturity Date. We will be required to make a final payment of 5.5% of the principal balance outstanding, payable on the earlier of (i) the Maturity Date, (ii) acceleration of any Term Loan, or (iii) the prepayment of the Term Loans.

We may use the proceeds from the Term Loans solely for working capital and to fund our general business requirements. Our obligations under the Loan Agreement are secured by a first priority security interest in substantially all of our current and future assets, other than our intellectual property. We have also agreed not to encumber our intellectual property assets, except as permitted by the Loan Agreement.

As of December 31, 2016, we had $20.0 million outstanding under the Term A Loan. The Term A Loan was recorded at its initial carrying value of $20.0 million, less debt issuance costs of approximately $0.2 million. In connection with

the Term A Loan, the debt issuance costs have been recorded as a debt discount on our balance sheets, which are being accreted to interest expense over the life of the Term A Loan using an effective interest rate of 8.98%. The exit fee is being accrued over the life of the Term A Loan through interest expense.

As of December 31, 2016, we were in compliance with all covenants under the Loan Agreement.

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Future principal payments for the Term A Loan due under the Loan Agreement are as follows (in thousands):

2017	$—
2018	5,000
2019	10,000
2020	5,000
	$20,000

11. Common Stock and Stockholders' Equity

Common Stock

As of December 31, 2016, there were 52,924,805 shares of common stock outstanding. Each share of common stock is entitled to one vote. The holders of the common stock are also entitled to receive dividends whenever funds are legally available and when declared by our Board of Directors.

Shares Reserved for Future Issuance

The following shares of common stock were reserved for future issuance as of December 31, 2016:

Common stock options outstanding	8,931,498
Common stock available for future grant under the 2012 Plan	718,299
Employee Stock Purchase Plan	1,594,452
Total common shares reserved for future issuance	11,244,249

The following table summarizes our stock option activity under all equity incentive plans for the year ended December 31, 2016 (shares and aggregate intrinsic value in thousands):

	Number of options	Weighted average exercise price	Weighted average remaining contractual term	Aggregate intrinsic value
Options outstanding at December 31, 2015	5,126	$ 8.91		
Granted	4,966	$ 4.93		
Exercised	(90)	$ 3.45		
Canceled/forfeited/expired	(1,071)	$ 9.32		
Options outstanding at December 31, 2016	8,931	$ 6.70	8.14	$ 34,680
Vested or expected to vest at December 31, 2016	8,278	$ 6.82	8.04	$ 31,463
Exercisable at December 31, 2016	2,882	$ 7.58	5.99	$ 9,688

The weighted average grant date fair value per share of employee stock options granted during the years ended December 31, 2016, 2015 and 2014 was $3.47, $7.47 and $8.37, respectively.

The total intrinsic value of stock options exercised was $0.2 million, $21.4 million and $12.1 million during the years ended December 31, 2016, 2015 and 2014, respectively. Cash received from the exercise of stock options was approximately $0.3 million, $6.7 million and $2.2 million for the years ended December 31, 2016, 2015 and 2014, respectively.

Stock-Based Compensation

The following table summarizes the weighted average assumptions used to estimate the fair value of stock options and performance stock awards granted to employees under our 2012 Equity Incentive Plan and 2015 Inducement Plan and the shares purchasable under our 2012 Employee Stock Purchase Plan during the periods presented:

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	Year ended December 31,		
	2016	2015	2014
Stock options			
Risk-free interest rate	1.5 %	1.8 %	1.8 %
Volatility	82.7%	78.9%	74.3%
Dividend yield	—	—	—
Expected term (years)	6.0	6.1	6.1
Performance stock options			
Risk-free interest rate	1.4 %	1.8 %	2.1 %
Volatility	82.4%	76.7%	69.6%
Dividend yield	—	—	—
Expected term (years)	5.9	6.0	6.3
Employee stock purchase plan shares			
Risk-free interest rate	0.5 %	0.1 %	0.1 %
Volatility	93.7%	76.1%	69.8%
Dividend yield	—	—	—
Expected term (years)	0.5	0.5	0.5

Risk-free interest rate - The risk-free interest rate assumption was based on observed interest rates appropriate for the expected term of the stock option grants.

Expected dividend yield - The expected dividend yield assumption was based on the fact that we have never paid cash dividends and have no present intention to pay cash dividends.

Expected volatility - The expected volatility assumption for the years ended December 31, 2016 and 2015 was based on the historical volatility of the trading price of our common stock. The expected volatility assumption for the year ended December 31, 2014 was based on a combination of volatility of a peer group of similar companies whose share prices were publicly available and the historical volatility of the trading price of our common stock. The peer group was developed based on companies in the biotechnology industry.

Expected term - The expected term represents the period of time that options are expected to be outstanding. Because we do not have sufficient historical exercise behavior data, we determine the expected life using the simplified method, which was an average of the contractual term of the option and its ordinary vesting period.

Forfeitures - We reduce stock-based compensation expense for estimated forfeitures. Forfeitures are estimated at the time of grant based upon historical information and revised, if necessary, in subsequent periods if actual forfeitures differ from those estimates. Our estimated forfeiture rates ranged from 3% to 7% for the years ended December 31, 2016 and 2015.

The following table summarizes the allocation of our stock-based compensation expense for all stock awards during the periods presented (in thousands):

	Year ended December 31,		
	2016	2015	2014
Research and development	$5,458	$8,075	$3,939
General and administrative	7,414	7,293	3,100
Total	$12,872	$15,368	$7,039

The total compensation cost related to non-vested awards not yet recognized was $12.3 million as of December 31, 2016. The weighted-average period over which this expense is expected to be recognized is approximately 1.5 years.

Employee Stock Purchase Plan

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In October 2012, we adopted the 2012 Employee Stock Purchase Plan ("2012 Purchase Plan"), which enables participants to contribute up to 15% of such participant's eligible compensation during a defined six-month period to purchase our common stock. The purchase price of common stock under the 2012 Purchase Plan will be the lesser of: (i) 85% of the fair market value of our common stock at the inception of the enrollment period or (ii) 85% of the fair market value of our common stock at the applicable purchase date. We issued 165,684 shares of common stock under the 2012 Purchase Plan for the year ended December 31, 2016. As of December 31, 2016, 321,184 shares of our common stock were issued and 1,594,452 shares of our common stock were reserved for future issuance and have been authorized for purchase under the 2012 Purchase Plan.

Inducement Plan

On July 17, 2015, the Company's Board of Directors adopted an Inducement Plan, which became effective immediately. Stockholder approval of the Inducement Plan was not required pursuant to Rule 5635 (c)(4) of the NASDAQ Listing Rules. The Inducement Plan initially reserved 1,000,000 shares of common stock and provides for the grant of NSOs that was used exclusively for grants to individuals that were not previously employees or directors of the Company, as an inducement material to the individual's entry into employment with the Company.

Under the Inducement Plan, options were granted with varying vesting terms, but typically vest over four years, with 25% of the total grant vesting on the first anniversary of the effective date of the option grant and the remaining grant vesting monthly thereafter over the following 36 months. All options granted under the Inducement Plan expire ten years from the date of grant.

As of December 31, 2016, all shares reserved under the Inducement Plan had been granted.

12. Defined Contribution Plan

In 2009, we established an employee 401(k) salary deferral plan ("401(k) Plan") covering all eligible employees. Active employees who are at least 18 years old and are not otherwise disqualified under the terms of the 401(k) Plan are eligible to participate. Employees may contribute up to 50% of their compensation per year (subject to a maximum limit prescribed by federal tax law). Under the 401(k) Plan, we may elect to match a discretionary percentage of employee contributions. We have elected to match 25% of employees' contributions up to 6% of the employees' eligible salary. We made $0.2 million in matching contributions for the year ended December 31, 2016 and $0.1 million for each of the years ended December 31, 2015 and 2014.

13. Income Taxes

The following table summarizes the components of our income tax (benefit) expense (in thousands):

	Year ended December 31,		
	2016	2015	2014
Current:			
Federal	$ —	$ —	$ —
State	1	1	1
	1	1	1
Deferred:			
Federal	(5)	(17)	—
State	—	(2)	—
	(5)	(19)	—
Income tax (benefit) expense	$ (4)	$ (18)	$ 1

The following is a reconciliation of the expected statutory federal income tax provision to our actual income tax provision (in thousands):

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	Year ended December 31,		
	2016	2015	2014
Expected income tax benefit at federal statutory tax rate	$(27,826)	$(18,960)	$(19,271)
State income taxes, net of federal benefit	(1,152)	(1,580)	(2,348)
Tax credits	(5,447)	(5,039)	(3,307)
Change in fair value of convertible note payable	—	616	4,120
Change in valuation allowance	31,990	23,216	20,047
Prior year true-up	(1,320)	110	(92)
Stock compensation	2,458	1,161	902
Reserve for uncertain tax positions	1,314	254	—
Other	(21)	204	(50)
Income tax (benefit) expense	$(4)	$(18)	$1

The following table summarizes the significant components of our deferred tax assets and liabilities (in thousands):

	December 31,	
	2016	2015
Deferred tax assets:		
Net operating loss carryovers	$70,739	$48,912
Research and development and other tax credits	22,613	15,148
Deferred revenue	735	1,210
Intangibles and property and equipment basis difference	—	2,097
Stock compensation expense	5,664	3,488
Other	4,679	1,129
Total deferred tax assets	104,430	71,984
Total deferred tax liabilities	(799)	(343)
Net deferred tax asset	103,631	71,641
Valuation allowance	(103,631)	(71,641)
Net deferred tax asset	$—	$—

For all periods presented, we have determined that it is more likely than not that our deferred tax asset will not be realized. Accordingly, we have recorded a valuation allowance to fully offset the net deferred tax asset of $103.6 million.

As of December 31, 2016, we had federal and California tax net operating loss carryforwards of $204.8 million and $173.2 million, respectively, which begin to expire in 2030 and 2031. At December 31, 2016, approximately $19.4 million and $19.4 million of the Federal and State net operating loss carryforwards, respectively, relate to stock option exercises, which will result in an increase to additional paid-in capital and a decrease in income taxes payable at the time when the tax loss carryforwards are utilized. Upon adoption of ASU 2016-09 in the first quarter of 2017, the balance of the unrecognized excess tax benefits will be reversed with the impact recorded to accumulated deficit, including any change to the valuation allowance as a result of the adoption. Due to the full valuation allowance on the U.S. deferred tax assets as of December 31, 2016, we do not expect any impact to the financial statements as a result of this adoption. As of December 31, 2016, we also had federal and California research and development tax credit carryforwards of $20.3 million and $6.9 million, respectively. The federal research and development tax credit carryforwards will begin to expire in 2029. The California research and development tax credit carryforwards are available indefinitely. As of December 31, 2016, we also had $0.2 million of Federal Alternative Minimum Tax Credit carryforwards that are available indefinitely.

The future utilization of our research and development credit carryforwards and net operating loss carryforwards to offset future taxable income may be subject to an annual limitation as a result of ownership changes that have occurred previously or may occur in the future. The Tax Reform Act of 1986 (the Act) limits a company’s ability to utilize certain tax credit carryforwards and net operating loss carryforwards in the event of a cumulative change in

ownerships in excess of 50% as defined in the Act.

The following table summarizes the changes in the amount of our unrecognized tax benefits (in thousands):

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	Year Ended December 31,		
	2016	2015	2014
Beginning balance of unrecognized tax benefits	$2,298	$1,853	$1,092
Increase (decrease) for prior year tax positions	1,991	(250)	(73)
Increase for current year tax positions	1,343	695	834
Total	$5,632	$2,298	$1,853

Included in unrecognized tax benefits of $5.6 million at December 31, 2016 was $3.7 million of tax benefits that, if recognized, would reduce our annual effective tax rate, subject to valuation allowance.

We are subject to taxation in the United States and California. Our tax years for 2009 and forward are subject to examination by the U.S. tax authorities and our tax years for 2009 and forward are subject to examination by the California tax authorities due to carryforward of unutilized net operating losses and research and development credits. It is our practice to recognize interest and/or penalties related to income tax matters in income tax expense. For the years ended December 31, 2016, 2015 and 2014, we have not recognized any interest or penalties related to income taxes.

14. Related Party Transactions

In September 2014, we entered into an agreement with Sanofi-Aventis Deutschland GmbH (“Sanofi Deutschland”), a contract manufacturing subsidiary of Sanofi, for the manufacture of certain drug substance requirements and other services to support our preclinical and clinical activities associated with the RG-012 program. Pursuant to this agreement, we may engage Sanofi Deutschland from time-to-time to manufacture RG-012 drug product on our behalf. Expenses incurred under the Sanofi agreement for services performed or out-of-pocket expenses were $0.9 million, $0.4 million and zero for the years ended December 31, 2016, 2015 and 2014, respectively.

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 years ended December 31, 2016 and 2015.

15. Selected Quarterly Financial Data (Unaudited)

The following financial information reflects all normal recurring adjustments, which are, in the opinion of management, necessary for a fair statement of the results of the interim periods. Summarized quarterly data for 2016 and 2015 are as follows (in thousands, except per share data):

	For the quarters ending			
	March 31	June 30	September 30	December 31
2016				
Revenues	$489	$483	$ 204	$ 18
Operating expenses	21,867	21,671	19,396	19,762
Net loss	(21,207)	(21,090)	(19,519)	(20,020)
Basic and diluted net loss per share	$(0.40)	$(0.40)	$ (0.37)	$ (0.38)
2015				
Revenues	$4,200	$3,834	$ 1,865	$ 10,860
Operating expenses	17,071	25,015	15,210	18,221
Net loss	(14,487)	(21,035)	(13,000)	(7,226)

Basic net loss per share(1)	$(0.29)	$(0.41)	$ (0.25)	$ (0.14)

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(1) Net loss per share is computed independently for each of the quarters presented. Therefore, the sum of the quarterly per-share calculations will not necessarily equal the annual per share calculation.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

None.

Item 9A. Controls and Procedures

Disclosure Controls and Procedures

We maintain disclosure controls and procedures that are designed to provide reasonable assurance that information required to be disclosed in our periodic and current reports that we file with the SEC is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our principal executive officer and principal financial and accounting officer, as appropriate, to allow timely decisions regarding required disclosure. In designing and evaluating the disclosure controls and procedures, management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable and not absolute assurance of achieving the desired control objectives. In reaching a reasonable level of assurance, management is required to apply its judgment in evaluating the cost-benefit relationship of possible controls and procedures. In addition, the design of any system of controls also is based in part upon certain assumptions about the likelihood of future events, and there can be no assurance that any design will succeed in achieving its stated goals under all potential future conditions; over time, controls may become inadequate because of changes in conditions, or the degree of compliance with policies or procedures may deteriorate. Because of the inherent limitations in a cost-effective control system, misstatements due to error or fraud may occur and not be detected.

As of December 31, 2016, we carried out an evaluation, under the supervision and with the participation of our management, including our principal executive officer and our principal financial and accounting officer, of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended. Based on this evaluation, our principal executive officer and our principal financial and accounting officer concluded that our disclosure controls and procedures were effective at the reasonable assurance level as of December 31, 2016.

Management's Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting as such term is defined in Exchange Act Rule 13a-15(f). Internal control over financial reporting is a process designed under the supervision and with the participation of our management, including our principal executive officer and principal financial and accounting officer, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with accounting principles generally accepted in the United States of America.

As of December 31, 2016, our management assessed the effectiveness of our internal control over financial reporting using the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission in Internal Control-Integrated Framework (2013 Framework). Based on this assessment, our management concluded that, as of December 31, 2016, our internal control over financial reporting was effective based on those criteria.

Changes in Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting as such term is defined in Exchange Act Rule 13a-15(f). An evaluation was performed under the supervision and with the participation of our management, including our chief executive officer and our principal financial and accounting officer, of any change in our internal control over financial reporting that occurred during our last fiscal quarter and that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting. That evaluation did not identify any change in our internal control over financial reporting that occurred during our latest fiscal quarter that has materially affected, or is reasonably likely to materially affect, our internal control over

financial reporting.

Item 9B. Other Information

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None.

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PART III

Item 10. Directors, Executive Officers and Corporate Governance

The information required by this item and not set forth below will be set forth in the section headed “Election of Directors” and “Executive Officers” in our Proxy Statement for our 2017 Annual Meeting of Stockholders, or Proxy Statement, to be filed with the SEC no later than May 1, 2017, and is incorporated herein by reference.

We have adopted a code of ethics for directors, officers (including our principal executive officer and principal financial and accounting officer) and employees, known as the Code of Business Conduct and Ethics. The Code of Business Conduct and Ethics is available on our website at http://www.regulusrx.com under the Corporate Governance section of our Investor Relations page. We will promptly disclose on our website (i) the nature of any amendment to the policy that applies to our principal executive officer, principal financial and accounting officer, or persons performing similar functions and (ii) the nature of any waiver, including an implicit waiver, from a provision of the policy that is granted to one of these specified individuals that is required to be disclosed pursuant to SEC rules and regulations, the name of such person who is granted the waiver and the date of the waiver.

Item 11. Executive Compensation

The information required by this item will be set forth in the sections headed “Executive Compensation” and "Director Compensation" in our Proxy Statement and is incorporated herein by reference.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information required by this item will be set forth under the heading “Security Ownership of Certain Beneficial Owners and Management" in our Proxy Statement and is incorporated herein by reference.

The information required by Item 201(d) of Regulation S-K will be set forth in the section headed “Equity Compensation Plan Information” in our Proxy Statement and is incorporated herein by reference.

Item 13. Certain Relationships and Related Transactions and Director Independence

The information required by this item will be set forth in the section headed “Transactions With Related Persons” in our Proxy Statement and is incorporated herein by reference.

Item 14. Principal Accounting Fees and Services

The information required by this item will be set forth in the section headed “Ratification of Selection of Independent Registered Public Accounting Firm” in our Proxy Statement and is incorporated herein by reference.

PART IV

Item 15. Exhibits, Financial Statement Schedules

Financial Statements. We have filed the following financial statements with this Annual Report:

	Page Number
Report of Independent Registered Public Accounting Firm	60
Balance Sheets	60
Statements of Operations and Comprehensive Loss	62
Statements of Stockholders’ Equity	63
Statements of Cash Flows	64
Notes to Financial Statements	65

Financial Statement Schedules. All schedules are omitted because they are not applicable or the required information is shown in the financial statements or notes thereto.

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Exhibits. For a list of exhibits filed with this Annual Report, refer to the Exhibit Index following the signature page to this Annual Report.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

Regulus Therapeutics Inc.

Date: March 2, 2017 By: /s/ Paul C. Grint
Paul C. Grint, M.D.
President and Chief Executive Officer
(Principal Executive Officer)

Date: March 2, 2017 By: /s/ Joseph P. Hagan
Joseph P. Hagan
Chief Operating Officer
(Principal Financial and Accounting Officer)

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Paul C. Grint, M.D. and Joseph P. Hagan as his true and lawful attorneys-in-fact, and each of them, with full power of substitution, for him in any and all capacities, to sign any amendments to this Annual Report on Form 10-K and to file the same, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done in and about the premises, as fully to all intents and purposes as he might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact, and either of them, or his or their substitute or substitutes may do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this Annual Report on Form 10-K has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Paul C. Grint Paul C. Grint, M.D.	Director, President & Chief Executive Officer (Principal Executive Officer)	March 2, 2017
/s/ Joseph P. Hagan Joseph P. Hagan	Chief Operating Officer (Principal Financial and Accounting Officer)	March 2, 2017
/s/ Stelios Papadopoulos Stelios Papadopoulos, Ph.D.	Chairman of the Board of Directors	March 2, 2017
/s/ David Baltimore David Baltimore, Ph.D.	Director	March 2, 2017

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Signature	Title	Date
/s/ Mark G. Foletta Mark G. Foletta	Director	March 2, 2017
/s/ William H. Rastetter William H. Rastetter, Ph.D.	Director	March 2, 2017
/s/ Douglas E. Williams Douglas E. Williams, Ph.D.	Director	March 2, 2017
/s/ Hugh Rosen Hugh Rosen, M.D., Ph.D.	Director	March 2, 2017

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EXHIBIT INDEX

Exhibit Number	Description
3.1	Amended and Restated Certificate of Incorporation of the Registrant (incorporated by reference to Exhibit 3.1 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-35670), filed with the SEC on August 3, 2016.
3.2	Amended and Restated Bylaws of the Registrant (incorporated by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K (File No. 001-35670), filed with the SEC on June 8, 2016).
4.1	Reference is made to Exhibits 3.1 and 3.2.
4.2	Form of Common Stock Certificate of the Registrant (incorporated by reference to Exhibit 4.1 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-183384), originally filed with the SEC on August 17, 2012).
10.1*	Form of Indemnity Agreement between the Registrant and its directors and officers (incorporated by reference to Exhibit 10.1 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-183384), originally filed with the SEC on August 17, 2012).
10.2*	Regulus Therapeutics Inc. 2009 Equity Incentive Plan, as amended, and Form of Stock Option Grant Notice, Option Agreement and Form of Notice of Exercise (incorporated by reference to Exhibit 10.2 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-183384), originally filed with the SEC on August 17, 2012).
10.3*	2012 Equity Incentive Plan and Form of Stock Option Agreement and Form of Stock Option Grant Notice thereunder (incorporated by reference to Exhibit 10.3 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-183384), originally filed with the SEC on August 17, 2012).
10.4*	Non-Employee Director Compensation Policy, as amended.
10.5*	2012 Employee Stock Purchase Plan (incorporated by reference to Exhibit 10.5 to the Registrant's Registration Statement on Form S-1, as amended, originally filed with the SEC on August 17, 2012).
10.6	Regulus Therapeutics Inc. Inducement Plan and Form of Stock Option Grant Notice, Form of Stock Option Agreement and Notice of Exercise thereunder (incorporated by reference to Exhibit 99.1 to the Company's Registration Statement on Form S-8 (File No. 333-206511), filed with the SEC on August 21, 2015).
10.7*	Amended and Restated Employment Agreement by and between the Registrant and Paul C. Grint, M.D., dated September 19, 2014 (incorporated by reference to Exhibit 99.3 to the Registrant's Current Report on Form 8-K (File No. 001-35670), filed with the SEC on September 19, 2014).
10.8*	Paul C. Grint, M.D., Yearly Discretionary Base Salary Increase, effective January 1, 2015 (incorporated by reference to Exhibit 10.15 to the Registrant's Annual Report on Form 10-K (File No. 001-35670), filed with the SEC on February 19, 2015).
10.9*	

	Paul C. Grint, M.D., Base Salary and Target Bonus Increases, effective June 1, 2015 (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-35670), filed with the SEC on August 5, 2015).
10.10*	Paul C. Grint, M.D. Yearly Discretionary Base Salary Increase, effective January 1, 2016 (incorporated by reference to Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-35670), filed with the SEC on May 3, 2016).
10.11*	Employment Agreement, effective January 1, 2016, by and between the Registrant and Joseph P. Hagan (incorporated by reference to Exhibit 10.10 to the Registrant's Annual Report on Form 10-K (File No. 001-35670), filed with the SEC on February 23, 2016).
10.12*	Employment Agreement, effective October 3, 2016, by and between the Registrant and Timothy M. Wright, M.D.

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10.13	Lease between the Registrant and BMR-John Hopkins Court LLC, a Delaware limited liability company, dated March 19, 2010 (incorporated by reference to Exhibit 10.9 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-183384), originally filed with the SEC on August 17, 2012).
10.14	First Amendment to Lease between the Registrant and BMR-John Hopkins Court LLC, a Delaware limited liability company, dated April 26, 2010 (incorporated by reference to Exhibit 10.10 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-183384), originally filed with the SEC on August 17, 2012).
10.15	Second Amendment to Lease between the Registrant and BMR-John Hopkins Court LLC, a Delaware limited liability company, dated January 26, 2011 (incorporated by reference to Exhibit 10.11 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-183384), originally filed with the SEC on August 17, 2012).
10.16	Third Amendment to Lease between the Registrant and BMR-3545-3575 John Hopkins LP, a Delaware limited partnership (formerly known as BMR-John Hopkins Court LLC), dated February 27, 2012 (incorporated by reference to Exhibit 10.12 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-183384), originally filed with the SEC on August 17, 2012).
10.17	Fourth Amendment to Lease between the Registrant and BMR-3545-3575 John Hopkins LP, a Delaware limited partnership (formerly known as BMR-John Hopkins Court LLC), dated November 19, 2012 (incorporated by reference to Exhibit 10.13 to the Registrant's Annual Report on Form 10-K (File No.001-35670), filed with the SEC on February 19, 2013).
10.18	Office Lease by and between the Registrant and ARE-SD Region No. 44, LLC (as successor in interest to Walton Torrey Owner B, L.L.C.), dated July 31, 2015 (incorporated by reference to Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-35670), filed with the SEC on August 5, 2015).
10.19†	Amended and Restated License and Collaboration Agreement among the Registrant, Alnylam Pharmaceuticals, Inc. and Ionis Pharmaceuticals, Inc. (formerly known as Isis Pharmaceuticals, Inc.), dated January 1, 2009 (incorporated by reference to Exhibit 10.17 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-183384), originally filed with the SEC on August 17, 2012).
10.20†	Amendment Number One to the Amended and Restated License and Collaboration Agreement among the Registrant, Alnylam Pharmaceuticals, Inc. and Ionis Pharmaceuticals, Inc. (formerly known as Isis Pharmaceuticals, Inc.), dated June 10, 2010 (incorporated by reference to Exhibit 10.18 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-183384), originally filed with the SEC on August 17, 2012).
10.21†	Amendment Number Two to the Amended and Restated License and Collaboration Agreement among the Registrant, Alnylam Pharmaceuticals, Inc. and Ionis Pharmaceuticals, Inc. (formerly known as Isis Pharmaceuticals, Inc.), dated October 25, 2011 (incorporated by reference to Exhibit 10.19 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-183384), originally filed with the SEC on August 17, 2012).
10.22†	Co-Exclusive License Agreement among the Board of Trustees of the Leland Stanford Junior University, Alnylam Pharmaceuticals, Inc. and Ionis Pharmaceuticals, Inc. (formerly known as Isis Pharmaceuticals, Inc.), dated August 31, 2005 (incorporated by reference to Exhibit 10.25 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-183384), originally filed with the SEC on August 17, 2012).

10.23	Assignment Agreement between the Registrant and Ionis Pharmaceuticals, Inc. (formerly known as Isis Pharmaceuticals, Inc.), dated July 13, 2009 (incorporated by reference to Exhibit 10.26 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-183384), originally filed with the SEC on August 17, 2012).
10.24†	License Agreement between the Registrant and Max-Planck-Innovation GmbH, dated June 5, 2009 (incorporated by reference to Exhibit 10.27 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-183384), originally filed with the SEC on August 17, 2012).
10.25†	Amended and Restated License Agreement among Max-Planck-Innovation GmbH, the Registrant, Ionis Pharmaceuticals, Inc. (formerly known as Isis Pharmaceuticals, Inc.) and Alnylam Pharmaceuticals, Inc., dated April 18, 2011 (incorporated by reference to Exhibit 10.28 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-183384), originally filed with the SEC on August 17, 2012).
10.26†	Exclusive Patent License Agreement between the Registrant and Bayerische Patent Allianz GmbH, dated May 18, 2010 (incorporated by reference to Exhibit 10.30 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-183384), originally filed with the SEC on August 17, 2012).

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10.27†	Non-Exclusive Technology Alliance and Option Agreement between the Registrant and Sanofi, dated June 21, 2010 (incorporated by reference to Exhibit 10.32 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-183384), originally filed with the SEC on August 17, 2012).
10.28†	Collaboration and License Agreement between the Registrant and AstraZeneca AB, dated August 14, 2012 (incorporated by reference to Exhibit 10.37 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-183384), originally filed with the SEC on August 17, 2012).
10.29†	Amendment No. 1 (to Collaboration and License Agreement) between the Registrant and AstraZeneca AB, dated April 30, 2013 (incorporated by reference to Exhibit 10.49 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-189607), originally filed with the SEC on June 26, 2013).
10.30†	Amendment Number Three to the Amended and Restated License and Collaboration Agreement among the Company, Alnylam Pharmaceuticals, Inc. and Isis Pharmaceuticals, Inc., dated August 2, 2013 (incorporated by reference to Exhibit 99.1 to the Registrant's Current Report on Form 8-K (File No. 001-35670), filed with the SEC on August 7, 2013).
10.31†	Second Amended and Restated Collaboration and License Agreement dated February 5, 2014 between the Registrant and Sanofi (incorporated by reference to Exhibit 10.54 to the Registrant's Annual Report on Form 10-K (File No. 001-35670), filed with the SEC on February 28, 2014).
10.32	Registration Rights Agreement dated February 5, 2014 between the Registrant and Aventis Holdings Inc. (incorporated by reference to Exhibit 99.3 to the Registrant's Current Report on Form 8-K (File No. 001-35670), filed with the SEC on February 5, 2014).
10.33†	Letter Agreement, dated as of January 30, 2015, by and between the Registrant and AstraZeneca AB (incorporated by reference to Exhibit 10.5 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-35670), filed with the SEC on May 8, 2015).
10.34†	Licensing Agreement, dated as of May 7, 2010, by and between the Registrant and ETH Zurich (incorporated by reference to Exhibit 10.32 to the Registrant's Annual Report on Form 10-K (File No. 001-35670), filed with the SEC on February 23, 2016).
10.35	Loan and Security Agreement, dated June 17, 2016, by and between the Registrant and Oxford Finance LLC (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-35670), filed with the SEC on August 3, 2016).
23.1	Consent of Independent Registered Public Accounting Firm.
24.1	Power of Attorney. Reference is made to the signature page hereto.
31.1	Certification of the Principal Executive Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934.
31.2	Certification of the Principal Financial Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934.

32.1**	Certification of the Principal Executive Officer and Principal Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101.INS	XBRL Instance Document.
101.SCH	XBRL Taxonomy Extension Schema Document.
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document.
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document.
101.LAB	XBRL Taxonomy Extension Label Linkbase Document.

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101.PREXBRL Taxonomy Extension Presentation Linkbase Document.

† We have requested or received confidential treatment for certain portions of this agreement, which have been omitted and filed separately with the SEC pursuant to Rule 406 under the Securities Act of 1933, as amended, or Rule 24b-2 of the Securities Exchange Act of 1934, as amended.

* Indicates management contract or compensatory plan.

** This certification is being furnished solely to accompany this annual report pursuant to 18 U.S.C. Section 1350, and is not being filed for purposes of Section 18 of the Securities Exchange Act of 1934 and is not to be incorporated by reference into any filing of the Registrant, whether made before or after the date hereof, regardless of any general incorporation language in such filing.